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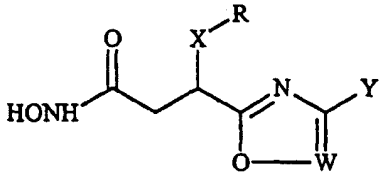
(54) Title: OX(ADI)AZOLYL-HYDROXAMIC ACIDS USEFUL AS PROCOLLAGEN C-PROTEINASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I) and their salts, solvates, prodrugs, etc., wherein the substituents have the values mentioned herein, are Procollagen C-Proteinase (PCP) inhibitors and have utility in conditions mediated by PCP.

WO 01/47901 A1

1/87

OX(ADI)AZOLYL-HYDROXAMIC ACIDS USEFUL AS PROCOLLAGEN C-PROTEINASE INHIBITORS

This invention relates to a certain class of compounds, and the pharmaceutically acceptable salts, solvates and prodrugs thereof, which inhibit Procollagen C-proteinase ("PCP"). They are therefore useful in the treatment of mammals having conditions alleviable by inhibition of PCP. Especially of interest is an antiscarring treatment for wounds.

Fibrotic tissues, including dermal scars, are characterised by excessive accumulation of extracellular matrix, mainly collagen type I. It is thought that inhibition of collagen deposition will reduce formation of scar tissue. Collagen is secreted as the precursor, procollagen, which is transformed into the insoluble collagen by cleavage of the C-terminal propeptide by PCP. PCP is a zinc-dependent metalloprotease which is secreted from TGF-β-activated fibroblasts belonging to the subfamily of astacin-like proteases and able to cleave the C-terminal peptide of types I, II and III procollagens. Furthermore, data suggest that PCP activates lysyl oxidase, an enzyme essential for the formation of covalent cross-links which stabilise the fibrous form of collagen. Therefore, inhibition of PCP may not only reduce collagen deposition but may also make collagen more accessible for degradation.

Collagen is integral to, among other things, the proper formation of connective tissue. Thus, the over- or under-production of collagen or the production of abnormal collagen (including incorrectly processed collagen) has been linked with numerous connective tissue diseases and disorders. Mounting evidence suggests that PCP is an essential key enzyme for the proper maturation of collagen (see for example International Patent Application publication number WO 97/05865).

The present invention relates to substances capable of inhibiting PCP activity in order to regulate, modulate and/or reduce collagen formation and deposition. More specifically, the invention relates to the use of compounds and pharmaceutical compositions thereof for the treatment of various conditions relating to production of collagen.

At present more than nineteen types of collagens have been identified. These collagens, including fibrillar collagen types I, II, III are synthesized as procollagen precursor molecules which contain amino- and carboxy-terminal peptide extensions. These peptide extensions, referred to as "pro-regions," are designated as N- and C- propeptides, respectively. The pro-regions are typically cleaved upon secretion of the procollagen triple helical precursor molecule from the cell to yield a mature triple helical collagen molecule. Upon cleavage, the "mature" collagen molecule is capable of association, for example, into highly structured

collagen fibers. See e.g., Fessler and Fessler, 1978, Annu. Rev. Biochem. 47:129-162; Bornstein and Traub, 1979, in: The Proteins (eds. Neurath, H. and Hill, R.H.), Academic Press, New York, pp. 412-632; Kivirikko et al., 1984, in: Extracellur Matrix Biochemistry (eds. Piez, K.A. and Reddi. A.H.), Elsevier Science Publishing Co., Inc., New York, pp. 83-118; Prockop and Kivirikko, 1984, N. Engl, J. Med. 311:376-383; Kuhn, 1987, in: Structure and Function of Collagen Types (eds. Mayne, R. and Burgeson, R.E.), Academic Press, Inc., Orlando, Florida, pp. 1-42.

An array of conditions has been associated with the inappropriate or unregulated production of collagen, including pathological fibrosis or scarring, including endocardial sclerosis, idiopathic interstitial fibrosis, interstitial pulmonary fibrosis, perimuscular fibrosis, Symmers' fibrosis, pericentral fibrosis, hepatitis, dermatofibroma, cirrhosis such as billary cirrhosis and alcoholic cirrhosis, acute pulmonary fibrosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney fibrosis/glomerulonephritis, kidney fibrosis/diabetic nephropathy, scleroderma/systemic, scleroderma/local, keloids, hypertrophic scars, severe joint adhesions/arthritis, myelofibrosis, corneal scarring, cystic fibrosis, muscular dystrophy (duchenne's), cardiac fibrosis, muscular fibrosis/retinal separation, esophageal stricture and Pyronie's disease. Further fibrotic disorders may be induced or initiated by surgery, including scar revision/plastic surgeries, glaucoma, cataract fibrosis, corneal scarring, joint adhesions, graft vs. host disease, tendon surgery, nerve entrapment, dupuytren's contracture, OB/GYN adhesions/fibrosis, pelvic adhesions, peridural fibrosis, restenosis. Other conditions where collagen plays a key role include burns. Fibrosis of lung tissue is also observed in patients suffering from chronic obstructive airways disease (COAD) and asthma. One strategy for the treatment of these diseases and conditions is to inhibit the overproduction and/or deposition and/or unregulation of collagen. Thus, identification and isolation of molecules which control, inhibit and/or modulate the production and deposition of collagen are of major medical interest.

Recent evidence suggests that PCP is the essential key enzyme that catalyzes the cleavage of the Procollagen C-propeptide. This has been demonstrated in fibrillar collagens, including type I, type II, and type III collagen.

PCP was first observed in the culture media of human and mouse fibroblasts (Goldberg et al., 1975, Cell 4:45-50; Kessler and Goldberg, 1978, Anal. Biochem. 86:463-469), and chick tendon fibroblasts (Duskin et al., 1978, Arch. Biochem. Biophys. 185:326-332; Leung et al., 1979, J. Biol, Chem. 254:224-232). An acidic proteinase which removes the C-terminal propeptides from type I procollagen has also been identified (Davidson et al., 1979, Eur. J. Biochem. 100:551).

A partially purified protein having PCP activity was obtained from chick calvaria in 1982. Njieha et al., 1982, Biochemistry 23:757-764. In 1985, chicken PCP was isolated, purified and characterized from conditioned media of chick embryo tendons. Hojima et al., 1985, J. Biol. Chem. 260:15996-16003. Murine PCP has been subsequently purified from media of cultured mouse fibroblasts. Kessler et al., 1986, Collagen Relat. Res. 6:249-266; Kessler and Adar, 1989, Eur. J. Biochem. 186:115-121. Finally, the cDNA encoding human PCP has been identified, as set forth in the above-referenced articles and references disclosed therein.

Experiments conducted with these purified forms of chick and mouse PCP have indicated that the enzyme is instrumental in the formation of functional collagen fibers. Fertala et al., 1994, J. Biol. Chem. 269:11584.

As a consequence of the enzyme's apparent importance to collagen production, scientists have identified a number of PCP inhibitors. See e.g., Hojima et al., supra. For example, several metal chelators have demonstrated activity as PCP inhibitors. Likewise, chymostatin and pepstatin A were found to be relatively strong inhibitors of PCP. Additionally, α_2-Macroglobuline, ovostatin, and fetal bovine serum appear to at least partially inhibit PCP activity.

Dithiothreitol, SDS, concanavalin A, Zn^{2+}, Cu^{2+}, and Cd^{2+} are similarly reported to be inhibitory at low concentrations. Likewise, some reducing agents, several amino acids, phosphate, and ammonium sulfate were inhibitory at concentrations of 1-10mM. Further, the enzyme was shown to be inhibited by the basic amino acids lysine and arginine (Leung et al., supra; Ryhänen et al., 1982, Arch. Biochem. Biophys. 215:230-235). Finally, high concentrations of NaCl or Tris-HCl buffer were found to inhibit PCP's activity. For example, it is reported that, with 0.2, 0.3, and 0.5M NaCl, the activity of PCP was reduced 66, 38, and 25%, respectively, of that observed with the standard assay concentration of 0.15M. Tris-HCl buffer in a concentration of 0.2-0.5M markedly inhibited activity (Hojima et al., supra). PCP activity and its inhibition have been determined using a wide array of assays. See e.g., Kessler and Goldberg, 1978, Anal. Biochem. 86:463; Njieha et al., 1982, Biochemistry 21:757-764. As articulated in numerous publications, the enzyme is difficult to isolate by conventional biochemical means and the identity of the cDNA sequence encoding such enzyme was not known until reported in the above referenced and related patent applications.

In view of its essential role in the formation and maturation of collagen PCP appears to be an ideal target for the treatment of disorders associated with the inappropriate or unregulated production and maturation of collagen. However, none of the inhibitors so far disclosed has

proven to be an effective therapeutic for the treatment of collagen-related diseases and conditions.

The identification of effective compounds which specifically inhibit the activity of PCP to regulate and modulate abnormal or inappropriate collagen production is therefore desirable and the object of this invention.

Matrix metalloproteases (MMPs) constitute a family of structurally similar zinc-containing metalloproteases, which are involved in the remodelling, repair and degradation of extracellular matrix proteins, both as part of normal physiological processes and in pathological conditions.

Another important function of certain MMPs is to activate other enzymes, including other MMPs, by cleaving the pro-domain from their protease domain. Thus, certain MMPs act to regulate the activities of other MMPs, so that over-production in one MMP may lead to excessive proteolysis of extracellular matrix by another, e.g. MMP-14 activates pro-MMP-2

During the healing of normal and chronic wounds, MMP-1 is expressed by migrating keratinocytes at the wound edges (U.K. Saarialho-Kere, S.O. Kovacs, A.P. Pentland, J. Clin. Invest. 1993, 92, 2858-66). There is evidence which suggests MMP-1 is required for keratinocyte migration on a collagen type I matrix in vitro, and is completely inhibited by the presence of the non-selective MMP inhibitor SC44463 ((N4-hydroxy)-N1-[(1S)-2-(4-methoxyphenyl)methyl-1-((1R)-methylamino)carbonyl)]-(2R)-2-(2-methylpropyl)butanediamide) (B.K. Pilcher, J.A. Dumin, B.D. Sudbeck, S.M. Krane, H.G. Welgus, W.C. Parks, J. Cell Biol., 1997, 137, 1-13). Keratinocyte migration in vivo is essential for effective wound healing to occur.

MMP-2 and MMP-9 appear to play important roles in wound healing during the extended remodelling phase and the onset of re-epithelialisation, respectively (M.S. Agren, Brit. J. Dermatology, 1994, 131, 634-40; T. Salo, M. Mäkänen, M. Kylmäniemi, Lab. Invest., 1994, 70, 176-82). The potent, non-selective MMP inhibitor BB94 ((2S,3R)-5-methyl-3-{[(1S)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl}-2-[(2-thienylthio)methyl]hexanohydroxamic acid, batimastat), inhibits endothelial cell invasion of basement membrane, thereby inhibiting angiogenesis (G. Tarboletti, A. Garofalo, D. Belotti, T. Drudis, P. Borsotti, E. Scanziani, P.D. Brown, R. Giavazzi, J. Natl. Cancer Inst., 1995, 87, 293-8). There is evidence that this process requires active MMP-2 and/or 9.

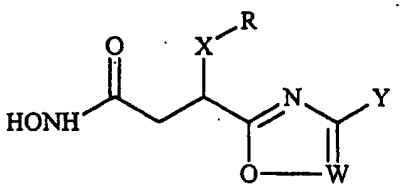
Thus PCP inhibitors which significantly inhibit MMPs 1 and/or 2 and/or 9 would be expected to impair wound healing. MMP-14 is responsible for the activation of MMP-2, and thus inhibition of MMP-14 might also result in impaired wound healing.

For recent reviews of MMPs, see Zask et al, Current Pharmaceutical Design, 1996, 2, 624-661; Beckett, Exp. Opin. Ther. Patents, 1996, 6, 1305-1315; and Beckett et al, Drug Discovery Today, vol 1(no.1), 1996, 16-26.

Alternative names for various MMPs and substrates acted on by these are shown in the table below (Zask et al, supra).

Enzyme	Other names	Preferred substrates
MMP-1	Collagenase-1, interstitial collagenase	Collagens I, II, III, VII, X, gelatins
MMP-2	Gelatinase A, 72kDa gelatinase	Gelatins, collagens IV, V, VII, X, elastin, fibronectin; activates pro-MMP-13
MMP-3	Stromelysin-1	Proteoglycans, laminin, fibronectin, gelatins.
MMP-7	Pump, Matrilysin	Proteoglycans, laminin, fibronectin, gelatins, collagen IV, elastin, activates pro-MMP-1 and -2 .
MMP-8	Collagenase-2, neutrophil collagenase	Collagens I, II, III
MMP-9	Gelatinase B, 92 kDa gelatinase	Gelatins, collagens IV, V, elastin
MMP-12	Macrophage metalloelastase	Elastin, collagen IV, fibronectin, activates pro-MMP-2 & 3.
MMP-13	Collagenase-3	Collagens I, II, III, gelatins
MMP-14	MT-MMP-1	Activates pro-MMP-2 & 13, gelatins
MMP-15	MT-MMP-2	unknown
MMP-16	MT-MMP-3	Activates pro-MMP-2
MMP-17	MT-MMP-4	unknown

According to one aspect of the present invention, there are provided compounds of formula (I):



(I)

wherein:

X is C_{1-6} alkylene or C_{2-6} alkenylene, each of which is optionally substituted by one or more fluorine atoms;

R is aryl or C_{3-8} cycloalkyl optionally substituted by one or more fluorine atoms;

W is N or CZ;

Y and Z are each independently H,
C_{1-4} alkyl (optionally substituted by one or more substituents independently selected from halogen, $S(O)_pR^6$, OR^5, $CONR^1R^2$, CO_2R^7 and aryl),
C_{1-4} alkanoyl optionally substituted by one or more halogen,
C_{1-4} alkoxycarbonyl optionally substituted by one or more halogen,
or $CONR^1R^2$;

R^1 and R^2 are each independently selected from H, C_{3-8} cycloalkyl, C_{1-4} alkyl (optionally substituted by C_{3-8} cycloalkyl, aryl, CO_2H, CO_2R^5 and/or NR^3R^4),
or R^1 and R^2 can be taken together with the nitrogen to which they are attached to represent a 4- to 6-membered heterocyclic ring optionally containing one or two further hetero atoms in the ring independently selected from N, O and S,
which heterocyclic ring is optionally benzo- or pyrido-fused,
and which heterocyclic ring is optionally substituted by C_{1-4} alkyl, CO_2H, CO_2R^5, aryl and/or NR^3R^4;

R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl or C_{1-4} alkoxycarbonyl optionally substituted by one or more halogen,
or R^3 and R^4 can be taken together with the nitrogen atom to which they are attached to represent a morpholine, piperidine, azetidine or piperazine (optionally N-substituted by C_{1-4} alkyl) moiety;

R^5 is C_{1-4} alkyl optionally substituted by CO_2R^7 or $CONR^3R^4$, or R^5 is aryl;

R^6 is C_{1-4} alkyl optionally substituted by one or more halogen, or aryl;

R^7 is H or R^6;

p is 0,1 or 2;

"Aryl" is a mono- or bicyclic aromatic carbocyclic or heterocyclic system comprising from 5 to 10 ring atoms, including up to 3 hetero-atoms selected from N, O and S,
where, if there is a N atom in the ring, it can be present as the N-oxide,
which ring system is optionally substituted by up to 3 substituents independently selected from halogen, C_{1-4} alkyl optionally substituted by one or more halogen, C_{1-4} alkoxy optionally substituted by one or more halogen, phenyl, pyridyl, CO_2H, $CONR^3R^4$, $CO_2(C_{1-4}$ alkyl), NR^3R^4, OH and $OC(O)(C_{1-4}$ alkyl);

and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

"Alkyl", "alkylene", "alkoxy", "alkanoyl", and "alkenylene" groups, including in groups incorporating said moieties, may be straight chain or branched where the number of carbon atoms allows.

Halogen is taken to mean fluorine, chlorine, bromine or iodine.

Pharmaceutically-acceptable salts are well known to those skilled in the art, and for example include those mentioned in the art cited above, and by Berge et al, in J.Pharm.Sci., 66, 1-19 (1977). Suitable acid addition salts are formed from acids which form non-toxic salts and include the hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate, bisulphate, phosphate, hydrogenphosphate, acetate, trifluoroacetate, gluconate, lactate, salicylate, citrate, tartrate, ascorbate, succinate, maleate, fumarate, gluconate, formate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, pamoate, camsylate, and p-toluenesulphonate salts.

Pharmaceutically acceptable base addition salts are well known to those skilled in the art, and for example include those mentioned in the art cited above, and can be formed from bases which form non-toxic salts and include the aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts, and salts of non-toxic amines such as diethanolamine.

Certain of the compounds of formula (I) may exist in one or more zwitterionic forms. It is to be understood that pharmaceutically acceptable salts includes all such zwitterions.

Certain of the compounds of formula (I), their salts, solvates, prodrugs, etc. may exist in one or more polymorphic forms. It is to be understood that the invention includes all such polymorphs.

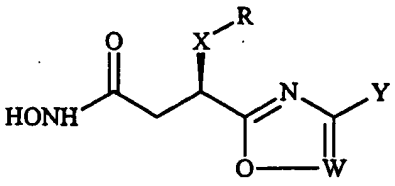
The compounds of formula (I), their salts, hydrates, prodrugs etc. can exhibit isotopic variation, e.g. forms with enriched ^2H, ^3H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, etc. may be prepared, for example by suitable

variation of the synthetic methods described herein using methods and reagents known in the art or routine modification thereof. All such isotopic variants are included in the scope of the invention.

Prodrug moieties are well-known to those skilled in the art (see for example the article by H Feres, in Drugs of Today, vol 19, no.9 (1983) pp.499-538, especially section A1), and for example include those specifically mentioned in A.A. Sinkula's article in Annual Reports in Medicinal Chemistry, vol 10, chapter 31, pp.306-326, herein incorporated by reference, and the references therein. Specific prodrug moieties which may be specifically mentioned are aliphatic-aromatic, carbonate, phosphate and carboxylic esters, carbamates, peptides, glycoside, acetals and ketals, tetrahydropyranyl and silyl ethers. Such prodrug moieties can be cleaved in situ, e.g. are hydrolysable in physiological conditions, to give compounds of formula (I).

Certain of the compounds of the formula (I) may exist as geometric isomers. The compounds of the formula (I) may possess one or more asymmetric centres, apart from the specified centres in formula (I), and so exist in two or more stereoisomeric forms. The present invention includes all the individual stereoisomers and geometric isomers of the compounds of formula (I) and mixtures thereof.

Preferably the compounds of formula (I) have the following stereochemistry (IA):



(IA)

Preferably, for compounds of formula (I) where W is CZ, at least one of Y and Z is H or C_{1-4} alkyl (optionally substituted by one or more halogen).

Preferably X is a linear C_{2-4} alkylene moiety optionally substituted by one or more fluorine atoms. Most preferably X is propylene.

Preferably R is C_{3-8} cycloalkyl optionally substituted by one or more fluorine atoms.

More preferably R is cyclobutyl or cyclohexyl optionally substituted by one or more fluorine atoms.

Yet more preferably R is cyclobutyl or cyclohexyl.

Most preferably R is cyclohexyl.

Preferably W is N, CH or CCH_3.

Most preferably W is N.

Preferably Z is H or C_{1-4} alkyl optionally substituted by one or more halogen atoms.

More preferably Z is H or methyl optionally substituted by one or more fluorine atoms.

Most preferably Z is H or methyl.

Preferably Y is C_{1-4} alkyl (optionally substituted by one or more substituents independently selected from halogen, $S(O)_pR^6$, OR^5, $CONR^1R^2$, CO_2R^7 and aryl), C_{1-4} alkoxycarbonyl, or $CONR^1R^2$.

More preferably Y is methyl, isopropyl, methoxymethyl, 2-methoxyethyl, (pyrrolidino)$COCH_2$, phenylsulphonylmethyl, 4-chlorophenoxymethyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, (imidazol-2-yl)methyl, $CO_2(C_{1-2}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl (optionally substituted by C_{3-6} cycloalkyl, aryl, CO_2H or CO_2R^5)), $CON(C_{1-4}$ alkyl)(C_{1-4} alkyl(optionally substituted by C_{3-6} cycloalkyl, aryl, CO_2H or CO_2R^5)), or $CONR^1R^2$ where R^1 and R^2 are taken together with the nitrogen to which they are attached to represent a 4- to 6-membered heterocyclic ring optionally containing one or two further hetero atoms in the ring independently selected from N, O and S,

and which heterocyclic ring is optionally benzo- or pyrido-fused,

and which heterocyclic ring is optionally substituted by C_{1-4} alkyl, CO_2H, CO_2R^5, aryl or NR^3R^4.

Yet more preferably Y is $CO_2C_2H_5$, $CONH_2$, $CONHCH_3$, $CONH(n\text{-}C_3H_7)$, $CONH(i\text{-}C_3H_7)$, (cyclopropyl)CH_2NHCO, (cyclobutyl)CH_2NHCO, (2-methoxyphenyl)CH_2NHCO, (4-methoxyphenyl)CH_2NHCO, (pyridin-2-yl)CH_2NHCO, $CONHCH_2CO_2H$, $CON(CH_3)CH_2CO_2CH_3$, $CON(CH_3)_2$, (4-dimethylaminopiperidinyl)CO, (3-morpholinoazetidinyl)CO, (4-(pyridin-4-yl)piperidino)CO, (pyridin-2-yl)$CH_2N(CH_3)CO$, $CON(CH_3)CH_2CO_2H$, (3-methoxycarbonylazetidinyl)CO, (3-carboxyazetidinyl)CO, methyl, isopropyl, methoxymethyl, 2-methoxyethyl, (pyrrolidino)$COCH_2$, phenylsulphonylmethyl, 4-chlorophenoxymethyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, (imidazol-2-yl)methyl, benzylaminocarbonyl, piperidinocarbonyl, (2,3-dihydroisoindol-2-yl)CO, (1,2,3,4-tetrahydroisoquinolin-2-yl)CO, morpholinocarbonyl, 4-methylpiperazinocarbonyl, (5-aza-1,2,3,4-tetrahydroisoquinolin-2-yl)CO or N-methylbenzylaminocarbonyl.

Most preferably Y is $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$.

A preferred group of compounds is that in which each substituent is as specified in the Examples below.

Another preferred group are the compounds are those of the Examples below (especially Examples 2,3 and 12) and the salts, solvates and prodrugs thereof.

A further aspect of the invention is a PCP inhibitor which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14.

A further aspect of the invention is the use of a PCP inhibitor which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 in medicine.

Further related to this aspect of the invention is the use of a PCP inhibitor which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 in the manufacture of an antiscarring medicament.

Further related to this aspect of the invention is a method of treating a condition mediated by PCP and in which MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14 have a beneficial effect, with an effective amount of PCP inhibitor which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14, an example of such a condition being a wound.

Preferably the PCP inhibitor mentioned in this aspect of the invention is selective against at least MMP-1, MMP-2 and MMP-9.

Most preferably the said PCP inhibitor is selective against MMP-1, MMP-2, MMP-9, and MMP-14.

Preferably the said selective PCP inhibitor has an IC_{50} vs. PCP of 0.5μM or lower, and selectivities vs. MMP-2 and MMP-9 of at least 30-fold, in the tests described herein.

Preferably the selective PCP inhibitor has an IC_{50} vs. PCP of 0.1μM or lower, and selectivities vs. MMP-1, MMP-2, MMP-9 and MMP-14 of at least 300-fold, in the tests described herein.

Another aspect of the invention is the use of the substances of formula (I) described herein, including the salts, solvates and prodrugs thereof, in medicine.

Another aspect of the invention is the use of the substances of formula (I) described herein, including the salts, solvates and prodrugs thereof, in the manufacture of an antiscarring medicament.

Another aspect of the invention is a pharmaceutical composition comprising a PCP inhibitor which is selective vs. MMP-1, MMP-2, MMP-9 and MMP-14, and a pharmaceutically acceptable diluent, carrier or adjuvant.

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I), salts thereof, solvates thereof and/or prodrugs thereof, and a pharmaceutically acceptable diluent, carrier or adjuvant.

Another aspect of the invention is the combination of a PCP inhibitor, preferably a compound of formula (I), or a salt, solvate or prodrug thereof, with another material useful in treating wounds, such as:

(i) a growth factor such as TGF-β-3 (Renovo), IGF-1 (Genentech), IGF-1 complex (Celtrix), KGF-2 or FGF-10 (Sumitomo), DWP-401/EGF (Daewoong) or SNK-863 (Sanwa Kagaku Kenkyusho);

(ii) a growth factor agonist such as Noggin (Regeneron);

(iii) a growth factor antibody/antisense material, such as those to: TGF-β-1 or 2 (Renovo, CaT), PDGF (Il Yang) or CTGF (Fibrogen);

(iv) a hormone such as DHEAS (Pharmadigm), ConXn / Relaxin (Connetics);

(v) an antibody to adhesion compounds such as ICAM-1 (Boehringer);

(vi) a MMP such as Collagenase ABC (BioSpecifics);

(vii) a barrier such as ADCON (Gliatech);

(viii) skin products such as artificial skin systems such as those based on DermaGraft (Advanced Tissue Sciences Inc.), INTEGRA Artificial Skin (Integra Life Sciences Holding Corp.), cell cultures such as Apligraf / Graftskin (Novartis), those developed by Cell Genesys Inc., AlloDerm (LifeCell) or matrix formulation products such as Argidene gel (Telios Pharmaceuticals Inc.);

(ix) a uPA inhibitor such as those disclosed in WO 99/01451;

(x) a MMP-3 inhibitor such as those disclosed in WO 99/35124, WO 99/29667;

A further aspect of the invention is the use of a substance according to the above definitions for the manufacture of a medicament for the treatment of a condition mediated by PCP.

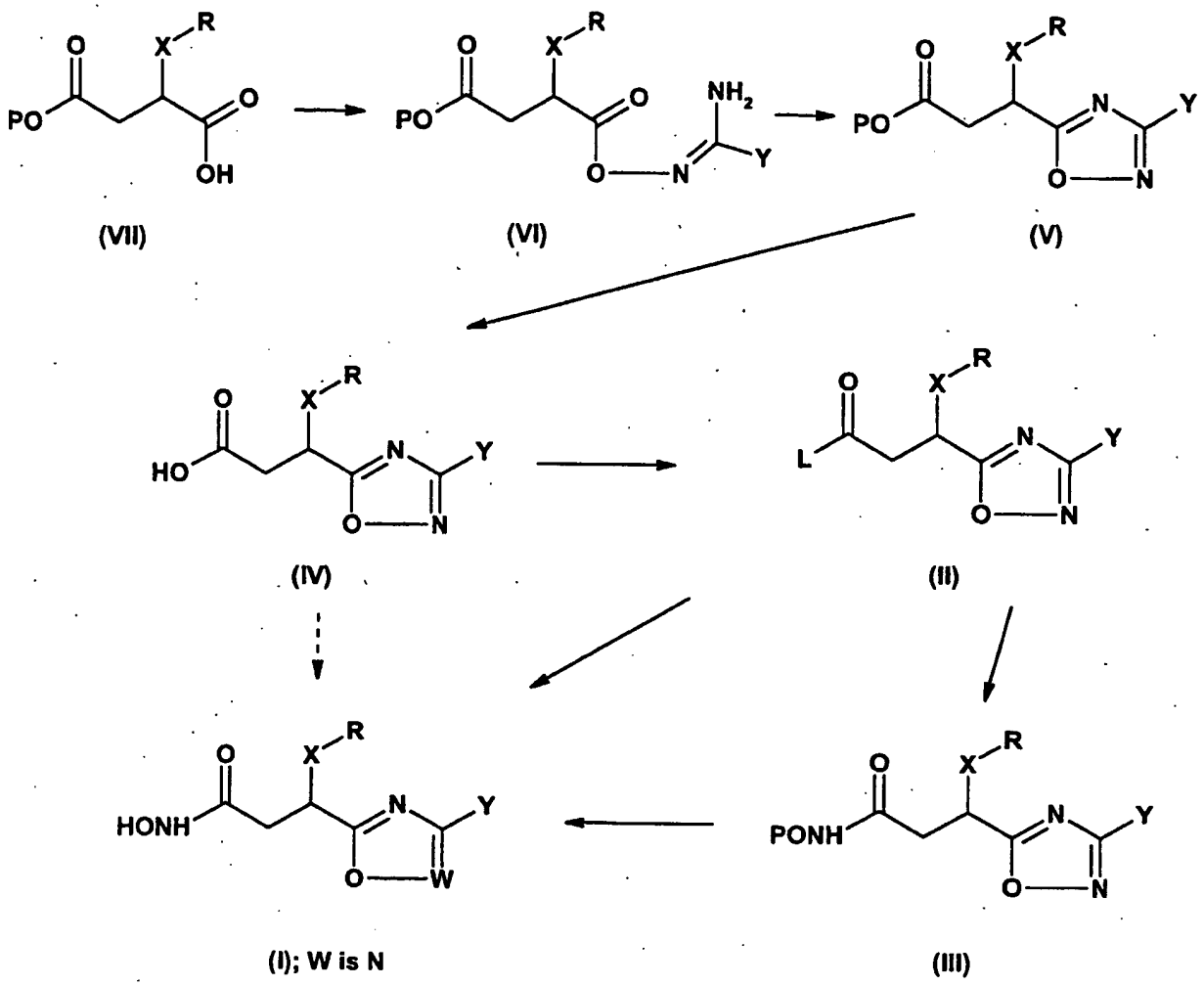
Yet another aspect of the invention is a method of treatment of a condition mediated by PCP comprising administration of a therapeutically-effective amount of a substance according to the above definitions.

It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of PCP-mediated conditions and diseases.

The invention further provides Methods for the production of compounds of the invention, which are described below and in the Examples and Preparations. The skilled man will appreciate that the compounds of the invention could be made by methods other than those specifically described herein, by adaptation of the methods herein described in the sections below and/or adaptation thereof, for example by methods known in the art. Suitable guides to synthesis, functional group transformations, use of protecting groups, etc. are, for example, "Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989), "Advanced Organic Chemistry" by J March, Wiley Interscience (1985), "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978), "Organic Synthesis - The Disconnection Approach" by S Warren, Wiley Interscience (1982), "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982), "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons Inc. (1999), and PJ Kocienski, in "Protecting Groups", Georg Thieme Verlag (1994), and any updated versions of said standard works.

In the Methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (I) above.

The compounds of formula (I), where W is N, can be prepared according to the chemistry outlined in the scheme below:



The hydroxamic acid compounds of formula (I) where W is N can be made by reaction of the corresponding activated acid derivative of formula (II), where L is a suitable leaving group, with hydroxylamine.

Suitable leaving groups are generally those which would leave in a more efficient manner than the hydroxide of the parent acid (IV), in a nucleophilic substitution reaction, such as a halide, C_{1-4} alkoxide optionally substituted by halogen, an alkylsulphonate such as methylsulphonate or mesylsulphonate, an arylsulphonate such as p-tosylsulphonate. Other suitable leaving groups are familiar to those working in the field of amino acid coupling.

Such compounds of formula (II) may be made via standard chemistry from the corresponding acid (IV). Compounds of formula (II) where L is a leaving group such as Cl, Br, I, $OCO(C_{1-4}$ alkyl optionally substituted by one or more halogen), mesylate, tosylate, and the like, can be made from

the corresponding compound of formula (II) where L is OH by conventional methods, including methods typified in e.g. Examples 2, etc.

The hydroxylamine used in this reaction is suitably generated in situ by treatment of a hydroxylamine salt such as the hydrochloride salt with a suitable base such as triethylamine. Suitably the reaction is carried out in a polar solvent such as DMF.
This reaction, leaving groups, solvents, reagents, etc. are exemplified below in Examples 1-4, 12-16, 18, 20-28, 30, 33-40 and 41.

Alternatively the compounds of formula (I) may be made from a NHO-protected compound of formula (III), where P is a suitable O-protecting group, by suitable deprotection.
Suitable O-protecting groups can be found in the text by Greene and Wuts, *supra*, and include trialkylsilyl (such as trimethylsilyl), benzyl, etc.
Compounds of formula (III) can be made in an analogous manner to the compounds of formula (I) from the compounds of formula (II), using a protected hydroxylamine $PONH_2$ or a suitable salt thereof in place of hydroxylamine itself or the hydroxylamine salt.
The deprotection method is determined by the protective group used, as is well known in the art. E.g. benzyl groups may be hydrogenated, suitably using a catalytic transfer hydrogenation method.
The reagents and conditions for reaction (III) -> (I) are typified in Examples 29, 31, and 32 below, and also in the other Examples where a protected hydroxylamine reagent (e.g. O-trimethylsilylhydroxylamine) was used (e.g.Examples 2, etc.), where conveniently the deprotection is carried out in the same vessel as the previous step.

Other methods of making hydroxamic acids (I) are known and may be used, e.g. those mentioned in the text by J.March, *supra*, chapters 0-54, 0-57 and 6-4, and relevant references therein.

Acids of formula (IV) may be made by deprotection of the O-protected species of formula (V).
Suitable O-protecting groups can be found in the chapter on O-protection in the book by Greene and Wuts, *supra*, and include C_{1-4} alkoxy such as t-butoxy (as typified in Preparation 4), benzyloxy, trialkylsilyloxy such as trimethylsilyloxy, etc..
The deprotection method is determined by the protective group used, as is well known in the art (see Greene and Wuts, *supra*). E.g. benzyl groups may be removed by hydrogenation, suitably using a catalytic transfer hydrogenation method, t-butyl groups may be removed by treatment with an acid such as trifluoroacetic acid, etc.

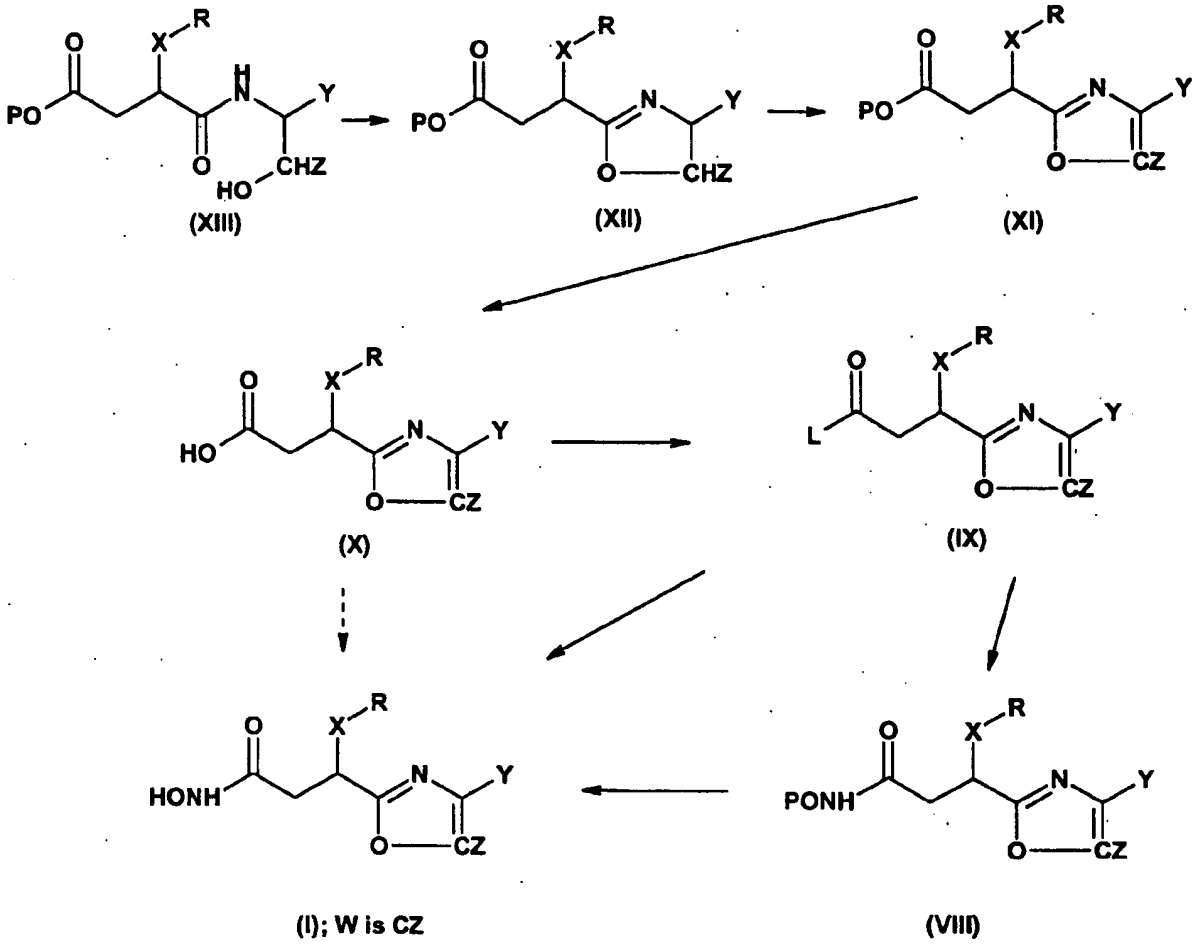
Compounds of formula (V), e.g. where P is a t-butoxy can be made for example by condensation reaction of a corresponding compound of formula (VI), for example by heating to elevated

temperature in an inert solvent such as in xylene at about 130°C, this reaction being typified by Preparation 3 below.

Compounds of formula (VI) can be made for example by coupling an acid of formula (VII) with a reagent of formula $C(NH_2)(Y)=NOH$, which is available via literature methods or adaptation thereof in a conventional manner, such as typified in methods described herein (e.g. see Preparation 2, etc.). Typically the condensation is carried out by adding a solution of the acid (VII) in a suitable inert solvent such as 1,4-dioxane to a suitable agent such as 1-hydroxybenzotriazole hydrate, followed by addition of a suitable coupling agent such as a carbodiimide coupling agent, e.g. N,N'-dicyclohexylcarbodiimide, then treatment with the reagent $C(NH_2)(Y)=NOH$. Suitably the coupling is carried out at ambient temperature.

Compounds of formula (VII) can be made by hydrogenation of the corresonding itaconate derivative, which in turn can be made by conventional methods such as the Stobbe condensation. Certain aspects of these preparations related to stereoselective preparation of certain intermediates, such as are disclosed in Preparation 1 - Route C, are novel and inventive and constitute a further aspect to this invention.

The compounds of formula (I), where W is CZ, can be prepared according to the chemistry outlined in the scheme below:



The hydroxamic acid compounds of formula (I) where W is CZ can be made by reaction of the corresponding activated acid derivative of formula (IX), where L⁻ is a suitable leaving group, with hydroxylamine. The leaving groups, reagents, etc. are the same as those mentioned above in relation to the corresponding compounds of formula (I) where W is N.

Such compounds of formula (IX) may be made via standard chemistry from the corresponding acid (X) using the same or similar chemistry to that outlined above in relation to the corresponding compounds of formula (II) where W is N (*supra*).

Alternatively the compounds of formula (I) may be made from a NHO-protected compound of formula (VIII), where P is a suitable O-protecting group, by suitable deprotection. Suitable O-protecting groups can be found in the text by Greene and Wuts, *supra*, and include trialkylsilyl (such as trimethylsilyl), benzyl, etc.

Compounds of formula (VIII) can be made in an analogous manner to the compounds of formula (II) from the compounds of formula (II), using a protected hydroxylamine $PONH_2$ or a suitable salt thereof in place of hydroxylamine itself or the hydroxylamine salt.

The deprotection method is determined by the protective group used, as is well known in the art. E.g. benzyl groups may be hydrogenated, suitably using a catalytic transfer hydrogenation method. The reagents and conditions for reaction (VIII) -> (I) are typified in Examples 29, 31, and 32 below, and also in the other Examples where a protected hydroxylamine reagent (e.g. O-trimethylsilylhydroxylamine) was used (e.g.Examples 2, etc.), where conveniently the deprotection is carried out in the same vessel as the previous step.

Other methods of making hydroxamic acids (I) are known and may be used, e.g. those mentioned in the text by J.March, *supra*, chapters 0-54, 0-57 and 6-4, and relevant references therein.

Acids of formula (X) may be made by deprotection of the O-protected species of formula (XI). Suitable O-protecting groups can be found in the chapter on O-protection in the book by Greene and Wuts, *supra*, and include C_{1-4} alkoxy such as t-butoxy (as typified in Preparation 4), benzyloxy, trialkylsilyloxy such as trimethylsilyloxy, etc..

The deprotection method is determined by the protective group used, as is well known in the art (see Greene and Wuts, *supra*). E.g. benzyl groups may be removed by hydrogenation, suitably using a catalytic transfer hydrogenation method, t-butyl groups may be removed by treatment with an acid such as trifluoroacetic acid, etc.

Compounds of formula (XI), e.g. where P is a t-butoxy group can be made for example by oxidation of a compound of formula (XII). Suitably the oxidation is carried out using copper (II) bromide with hexamethylenetetramine and a base such as DBU. The reagents, conditions, etc. are typified in Preparation 62 below.

Compounds of formula (XII) may be made by condensation of compounds of formula (XIII), for example by treatment of the compound of formula (XIII) with s suitable agent such as Burgess Reagent, in an anhydrous solvent such as THF. This reaction is typified in Preparation 61 below.

Compounds of formula (XIII) may be made by condensation of the acid of formula (II) above with an agent of formula $NH_2CH(Y)CH(Z)OH$, as typified in Preparation 60 below. Compounds of formula $NH_2CH(Y)CH(Z)OH$ are available commercially, from the literature or by routine modification thereof.

Certain compounds of formula (I) may be interconverted into other compounds of formula (I) - for Example where Y is an acid, this can be converted to an ester and vice versa - typified in Examples 17 and 19 below.

It will be apparent to those skilled in the art that other protection and subsequent deprotection regimes during synthesis of a compound of the invention may be achieved by conventional techniques, for example as described in the volumes by Greene and Wuts, and Kocienski, *supra*.

Where desired or necessary the compound of formula (I) is converted into a pharmaceutically acceptable salt thereof. A pharmaceutically acceptable salt of a compound of formula (I) may be conveniently be prepared by mixing together solutions of a compound of formula (I) and the desired acid or base, as appropriate. The salt may be precipitated from solution and collected by filtration, or may be collected by other means such as by evaporation of the solvent.

Certain compounds of the invention may be interconverted into certain other compounds of the invention by methods mentioned in the Examples and Preparations, and well-known methods from the literature.

Compounds of the invention are available by either the methods described herein in the Methods, Examples and Preparations or suitable adaptation thereof using methods known in the art. It is to be understood that the synthetic transformation methods mentioned herein may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound.

The compounds, salts, solvates and prodrugs of the invention may be separated and purified by conventional methods.

Separation of diastereomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereomeric salts formed by reaction of the corresponding racemate with a suitably optically active acid or base. In certain cases preferential crystallisation of one of the enantiomers can occur from a solution of a mixture of enantiomers, thus enriching the remaining solution in the other enantiomer.

For human use, the compounds of formula (I) or their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. The compound or salt could be incorporated into capsules or tablets for targetting the colon or duodenum via delayed dissolution of said capsules or tablets for a particular time following oral administration. Dissolution could be controlled by susceptibility of the formulation to bacteria found in the duodenum or colon, so that no substantial dissolution takes places before reaching the target area of the gastrointestinal tract. The compounds or salts can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution or suspension which may contain other substances, for example, enough salt or glucose to make the solution isotonic with blood. They can be administered topically, or transdermally, in the form of sterile creams, gels, suspensions, lotions, ointments, dusting powders, sprays, foams, mousses, drug-incorporated dressings, skin patches, ointments such as petrolatum or white soft paraffin based ointments or via a skin patch or other device. They could be administered directly onto a wound. They could be incorporated into a coated suture. For example they can be incorporated into a lotion or cream consisting of an aqueous or oily emulsion of mineral oils; sorbitan monostearate; polysorbate 60; cetyl esters wax; cetearyl alcohol; 2-octyldodecanol; benzyl alcohol; water; polyethylene glycols and/or liquid paraffin, or they can be incorporated into a suitable ointment consisting of one or more of the following - mineral oil; liquid petrolatum; white petrolatum; propylene glycol; polyoxyethylene polyoxypropylene compound; emulsifying wax and water, or as hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA, CFC, CO_2 or other suitable propellant, optionally also including a lubricant such as sorbitan trioleate, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings. The compound or salt could also be administered intraocularly for ophthalmic use e.g. in a lens implant or as an eye drop with appropriate buffers, viscosity modifiers (e.g. cellulose or polyacrylate derivatives), preservatives (e.g. benzalkonium chloride (BZK)) and agents to adjust tonicity (e.g. sodium chloride). Such formulation techniques are well-known in the art.

For certain uses, vaginal, rectal and nasal (e.g. by inhalation of a dry powder or aerosol) administration would be suitable.

All such formulations may also contain appropriate stabilisers and preservatives.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of formula (I) or their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5 mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time as appropriate.

For topical administration to human patients with acute/surgical wounds or scars, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.01 to 50mg/ml, preferably from 0.3 to 30 mg/ml.

The dosage will vary with the size of the wound, whether or not the wound is open or closed or partially closed, and whether or not the skin is intact.

The physician in any event will determine the actual dosage which will be most suitable for a an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can of course be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Biological Test Methods

PCP Inhibition

In order to determine potency of PCP inhibitors a fluorogenic PCP cleavage assay was used. This assay is based on the template of Beekman et al. (FEBS Letters (1996), 390: 221-225) using a fluorogenic substrate. The substrate (Dabcyl-Arg-Tyr-Tyr-Arg-Ala-Asp-Asp-Ala-Asn-Val-Glu(EDANS)-NH_2) contains the cleavage site of human PCP (Hojima et al., J Biol Chem (1985), 260: 15996-16003). Human PCP has been purified from supernatant of stable transfected CHO cells using hydrophobic interaction column followed by Superdex 200 gel filtration. 4 µg total protein of this enzyme preparation was incubated with various concentrations of the substance to be tested and 3x 10^{-6} M substrate in assay buffer (50 mM Tris-Base, pH 7.6 containing 150 mM NaCl, 5 mM $CaCl_2$, 1µM $ZnCl_2$ and 0.01 % Brij 35). The assay was performed in 96-well black fluorimeter plates and fluorescence was read continuously in a fluorimeter over 2.5 hours (λ_{ex} = 340 nm, λ_{em} = 485 nm) at a constant 37°C with shaking. Release of the fluorogenic signal

was in linear correlation to PCP activity. Reading of the mean velocity from 30 min after start of experiment until 2.5 hours was calculated by the Biolise software. IC_{50} values were calculated by plotting % inhibition values against compound concentration using Tessela add in for Excel spreadsheet.

MMP Inhibition

The ability of compounds to inhibit the cleavage of fluorogenic peptides by MMPs 1, 2, 9, and 14 is described below.

The assays for MMPs 2, 9, and 14 are based upon the original protocol described by Knight et al. (Fed.Euro.Biochem.Soc., 296 (3), 263-266; 1992) with the slight modifications given below.

Inhibition of MMP-1

(i) Enzyme Preparation

Catalytic domain MMP-1 was prepared at Pfizer Central Research. A stock solution of MMP-1 (1μM) was activated by the addition of aminophenylmercuric acetate (APMA), at a final concentration of 1mM, for 20 minutes at 37°C. MMP-1 was then diluted in Tris-HCl assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnSO_4$, 0.05% Brij 35) pH 7.5 to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

(ii) Substrate

The fluorogenic substrate used in this assay was Dnp-Pro- -cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys(N-Me-Ala)-NH_2 as originally described by Bickett et al (Anal. Biochem, 212, 58-64, 1993). The final substrate concentration used in the assay was 10μM.

(iii) Determination of Enzyme Inhibition

Test compounds were dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence (substrate cleavage) using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 355nm and emission wavelength of 440nm. The potency of inhibitors was measured from the amount of substrate cleavage obtained using a range of test compound concentrations, and, from the resulting dose-

response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-2 and MMP-9

(i) Enzyme Preparation

Catalytic domain MMP-2 and MMP-9 were prepared at Pfizer Central Research. A stock solution of MMP-2 / MMP-9 (1 M) was activated by the addition of aminophenylmercuric acetate (APMA). For MMP-2 and MMP-9, a final concentration of 1mM APMA was added, followed by incubation for 1 hour at 37°C. The enzymes were then diluted in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM $CaCl_2$ and 0.16% Brij 35, pH 7.5), to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

(ii) Substrate

The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 (Bachem Ltd, Essex, UK) as originally described by Nagase et al (J.Biol.Chem., 269(33), 20952-20957, 1994). This substrate was selected because it has a balanced hydrolysis rate against MMPs 2 and 9 (k_{cat} / k_m of 54,000, 59,400 and 55,300 s^{-1} M^{-1} respectively). The final substrate concentration used in the assay was 5μM.

(iii) Determination of Enzyme Inhibition

Test compounds were dissolved in dimethyl sulphoxide and diluted with test buffer solution (as above) so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 328nm and emission wavelength of 393nm. The potency of inhibitors was measured from the amount of substrate cleavage obtained using a range of test compound concentrations, and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-14

(i) Enzyme Preparation

Catalytic domain MMP-14 was purchased from Prof. Tschesche, Department of Biochemistry, Faculty of Chemistry, University of Bielefeld, Germany. A 10 M enzyme stock solution was

activated for 20 minutes at 25°C following the addition of 5 g/ml of trypsin (Sigma, Dorset, UK). The trypsin activity was then neutralised by the addition of 50 g/ml of soyabean trypsin inhibitor (Sigma, Dorset, UK), prior to dilution of this enzyme stock solution in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM $CaCl_2$ and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

(ii) Substrate

The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (Bachem Ltd, Essex, UK) as described by Will et al (J.Biol.Chem., 271(29), 17119-17123, 1996). The final substrate concentration used in the assay was 10μM.

Determination of enzyme inhibition by test compounds was performed in the same manner as described for MMPs-2 and -9 above.

The compounds of Examples 1-40 and 42-58 had PCP IC_{50} values of 0.5μM and below, and the compounds of Examples 1-40, 43, 44 and 46 had selectivities vs MMP-2 of more than 100-fold.

All references mentioned herein in this text are incorporated by reference in their entirety.

EXAMPLES AND PREPARATIONS

Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data were obtained using Varian Unity Inova-400, Varian Unity Inova-300 or Bruker AC300 spectrometers and are quoted in parts per million from tetramethylsilane. Mass spectral (MS) data were obtained on a Finnigan Mat. TSQ 7000 or a Fisons Instruments Trio 1000. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. Infra red (IR) spectra were measured using a Nicolet Magna 550 Fourier transform infra-red spectrometer. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt. Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualised using UV light, 5% aqueous potassium permanagate or Dragendorff's reagent (oversprayed with aqueous sodium nitrite). Thermal analyses by Differential Scanning Calorimetry (DSC) and ThermoGravimetric Analysis (TGA) were obtained using Perkin Elmer DSC7 and TGA7. Moisture sorption characteristics were recorded using Surface Measurement Systems Ltd. Automated Water Sorption Analyser DVS 1. Water content was determined on a Mitsubishi CA100 (Coulometric Karl Fisher Titrator). Powder X-ray diffraction (PXRD) pattern was determined using a Siemens D5000 powder X-ray diffractometer fitted with an automatic sample

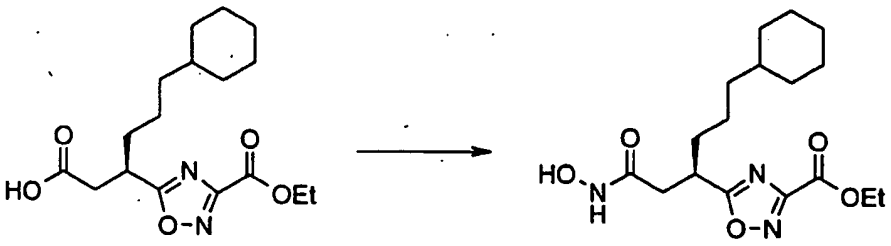
changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. Other measurements were taken using standard equipment. Hexane refers to a mixture of hexanes (hplc grade) b.p. 65-70°C. Ether refers to diethyl ether. Acetic acid refers to glacial acetic acid. 1-Hydroxy-7-aza-1H-1,2,3-benzotriazole (HOAt), N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethaninium hexafluorophosphate N-oxide (HATU) and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) were purchased from PerSeptive Biosystems U.K. Ltd. "DIPE" refers to diisopropyl ether. Reverse-phase silica gel for flash chromatography was obtained from Fluka (Fluka 100, C_{18}, 40-63µ). Pentane refers to High Performance Liquid Chromatography (HPLC) grade n-pentane (b.pt.35-37°C). Nomenclature has been allocated using a program available from IUPAC. Standard abbreviations are used throughout, e.g. "Me" is methyl, "Et" is ethyl, "Pr" is propyl, "Ph" is phenyl, etc. It was noticed that during certain repetitions of the methods disclosed in the Examples and Preparations that some racemisation appeared to have taken place. It was found in some cases that specific desired enantiomers can be separated from mixtures thereof by routine methods such as by differential crystallisation.

[a]HPLC autopurification performed using 2 columns - Phenomonex LUNA C8 150x21.2mm, 10µm and Phenomonex MAGELLEN C18 150x21.2mm, 5µm, eluting with a gradient system of organic solvent [ammonium acetate (aq) 100mM : acetonitrile (1 : 9)] : aqueous solvent [ammonium acetate (aq) 100mM : acetonitrile (9 : 1)]

[b] HPLC autopurification performed using 2 columns - Phenomonex LUNA C8 150x21.2mm, 10µm and Phenomonex MAGELLEN C18 150x21.2mm, 5µm, eluting with a gradient system of organic solvent (acetonitrile) : aqueous solvent (0.1% aqueous trifluoroacetic acid)

Example 1 :

Ethyl 5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxylate



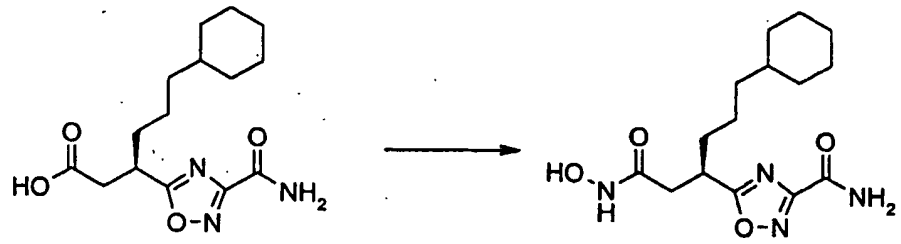
A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (140mg, 0.41mmol) and N,N-diisopropylethylamine (320µl, 2.07mmol) in N,N-dimethylformamide (5ml) was treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (235mg, 0.61mmol) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 30 minutes. Hydroxylamine hydrochloride (113mg, 0.61mmol) was then added and the mixture was stirred at room temperature for 20 hours. The mixture was poured into hydrochloric acid (1M, 20ml) and extracted with ethyl acetate (x3). The combined organic layers were washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99.5 : 0.5) gradually changing to dichloromethane : methanol (97 : 3) to afford the title compound as a yellow oil (62mg).

MS : 354 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.52 (2H, m), 3.70 (1H, br m), 2.94-2.52 (2H, br m), 1.96-1.00 (18H, m), 0.85 (2H, m).

Example 2 (a):

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-3-[3-(aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid (Preparation 6) (6.00g, 19.42mmol) in anhydrous tetrahydrofuran (200ml) was cooled to 0°C then treated with N-methylmorpholine (2.40ml, 22.0mmol) and isobutyl chloroformate (2.8ml, 22.0mmol) and stirred under a nitrogen atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (7.0ml, 60.0mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (50ml) and stirred for a further 30 minutes. This mixture was partitioned between ethyl acetate and water. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered

and the solvent removed under reduced pressure. The solid was recrystallised from isopropyl acetate (500ml) to afford the title compound as a white solid (4.46g). Chiral HPLC analysis indicated this material to be 87.6% ee. A sample of this material (2.9g) was dissolved in ethyl acetate (450ml) at reflux then allowed to cool. The precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure to afford a white solid, which was then recrystallised from isopropyl acetate (120ml) to afford the title compound (1.42g). Chiral HPLC analysis showed this material to be 98.3% ee.

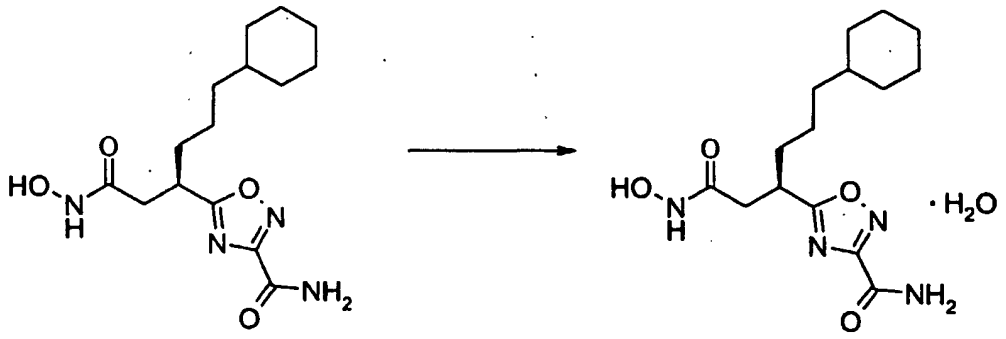
MS : 323 (MH^+)

^{1}H-NMR (DMSO-d_6) δ : 10.50 (1H, br s), 8.81 (1H, br s), 8.26 (1H, br s), 8.05 (1H, br s), 3.47 (1H, m), 2.56-2.39 (2H, m), 1.73-1.46 (7H, m), 1.27-0.99 (8H, m), 0.80 (2H, m).

Analysis : Found C, 52.76; H, 7.64; N, 16.34%; $C_{15}H_{24}N_4O_4.H_2O$ requires C, 52.62; H, 7.65; N, 16.36%

MPt.: 136-138°C

Example 2(b): 5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide monohydrate



A solution of 5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide (1.58 Kg, 4.86 mol) in tetrahydrofuran (15 litres) was heated to 40°C and demineralised water (26 litres) was added to give a hazy solution. The mixture was allowed to cool to ambient temperature where it was stirred for 24 hours. The mixture was cooled to 5°C and stirred for 1 hour. The precipitate was collected by filtration and dried *in vacuo* (38°C, 100 mbar) to afford the title compound as a colourless solid (1.37 Kg).

^{1}H-NMR (DMSO-d_6) δ : 10.50 (1H, br s), 8.81 (1H, br s), 8.26 (1H, br s), 3.47 (1H, m), 2.56-2.39 (2H, m), 1.73-1.46 (7H, m), 1.27-0.99 (8H, m), 0.80 (2H, m)

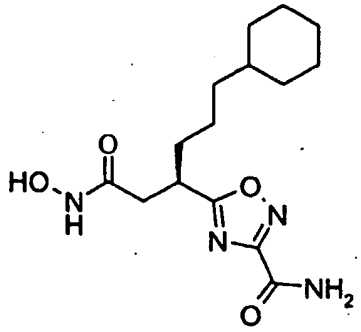
Water Content (Coulometric Karl Fisher): 5.0%

Dynamic Vapour Sorption: 5.17% w/w @ 20%RH (30°C), 4.84% w/w @ 2%RH (30°C), significant dehydration below 1%RH (30°C).

TGA (Weight Loss): 24°C-117°C = 4.93%

117°C-160°C = 0.26%

Example 2(c): 5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide (anhydrous)



5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide (3.20 g, 9.86 mmol) was dissolved in ethyl acetate (80 ml) at reflux. The mixture was allowed to cool to ambient temperature, stirred for 3 hours. The precipitate was collected by filtration and dried *in vacuo* (40-45°C, 48 hours) to afford the title compound as a colourless solid (2.40 g).

^{1}H-NMR (DMSO-d_6) δ : 10.50 (1H, br s), 8.81 (1H, br s), 8.26 (1H, br s), 3.47 (1H, m), 2.56-2.39 (2H, m), 1.73-1.46 (7H, m), 1.27-0.99 (8H, m), 0.80 (2H, m)

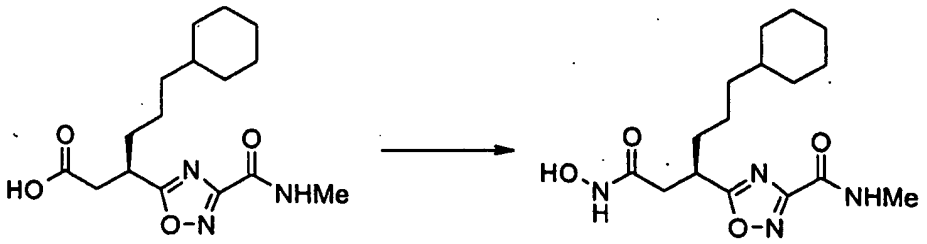
Dynamic Vapour Sorption: 0.18% w/w @ 15%RH (30°C), 0.23% w/w @ 30%RH (30°C), 0.34% w/w @ 45% RH (30°C). Title compound hydrates slowly at 60%RH (30°C) converting to the monohydrate (XRD used to confirm), eventually equilibrates at 5.3% w/w at 90%RH (30°C).

TGA (Weight Loss): 25°C-91°C = 0.22%

91°C-138°C = 0.33%

Example 3 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-methyl-1,2,4-oxadiazole-3-carboxamide

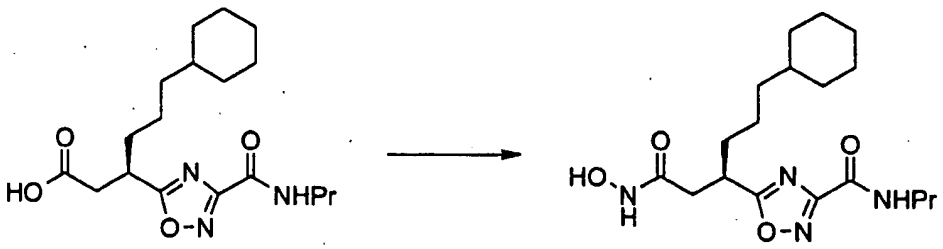


A solution of (3R)-6-cyclohexyl-3-{3-[(methylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 8) (285mg, 0.88mmol) and N-methylmorpholine (110µl, 1.00mmol) in anhydrous tetrahydrofuran (10ml) was cooled to 0°C, treated with isobutyl chloroformate (130µl, 1.00mmol) and stirred under a nitrogen atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (130µl, 1.06mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with aqueous citric acid solution (10% w/v, 10ml) and stirred for 2 hours. This mixture was diluted with water and extracted with ethyl acetate (x3). The combined organic layers were washed sequentially with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The solid was then recrystallised from hexane : ethyl acetate to afford the title compound as a white solid (130mg).

^{1}H-NMR (DMSO-d_6) δ : 10.48 (1H; br s), 8.87 (1H, m), 8.77 (1H, br s), 3.48 (1H, m), 3.19 (2H, m), 2.16 (1H, m), 1.87 (1H, m), 1.57 (9H, m), 1.14 (8H, m), 0.80 (5H, m).

Example 4 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-propyl-1,2,4-oxadiazole-3-carboxamide



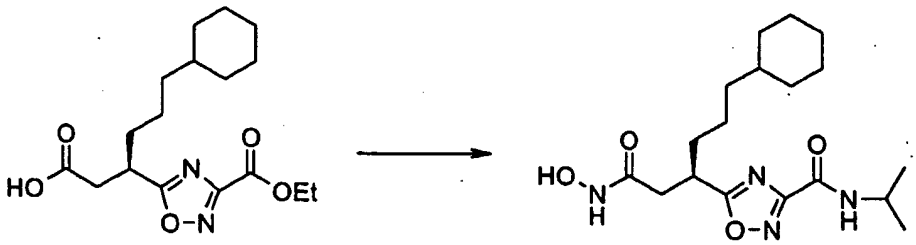
A solution of (3R)-6-cyclohexyl-3-{3-[(propylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 9) (66mg, 0.18mmol) and N,N-diisopropylethylamine (31µl, 0.18mmol) in N-methyl-2-pyrrolidinone (3ml) was treated with O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate (102mg, 0.27mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour. N,N-diisopropylethylamine (93µl, 0.54mmol) was then added, followed by hydroxylamine hydrochloride (37.5mg, 0.54mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate and pH 7 aqueous buffer. The combined organic layers were washed sequentially with aqueous citric acid solution (5% w/v) and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (90 : 10) gradually changing to dichloromethane : ethyl acetate (0 : 100) then to dichloromethane : methanol (95 : 5) to afford the title compound as an oil (31mg).

MS : 367(MH^+)

^{1}H-NMR (DMSO-d_6) δ : 10.48 (1H, br s), 8.87 (1H, br t), 8.76 (1H, br s), 3.47 (1H, m), 3.19 (2H, m), 2.16 (1H, m), 1.88 (1H, m), 1.76-1.43 (9H, m), 1.30-1.00 (8H, m), 0.90-70 (5H, m).

Example 5 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-isopropyl-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of isopropylamine (434mg, 7.35mmol) in ethanol (2ml) and the resulting mixture was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 10ml) then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (531mg) was then

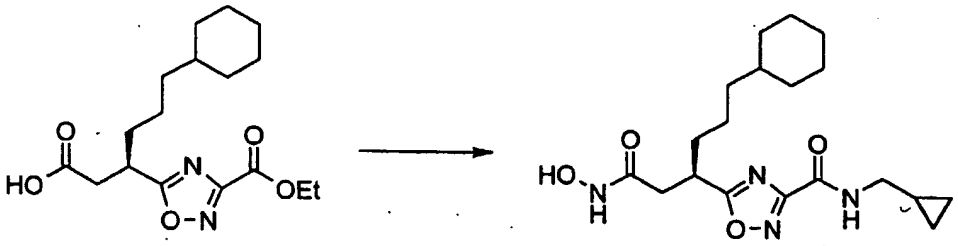
dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (180µl, 1.63mmol) and isobutyl chloroformate (210µl, 1.62mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (220µl, 1.80mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water (5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by reverse phase HPLC[a] to afford the title compound as a foam (43mg).

MS : 367(MH^+), 389 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 9.06 (1H, br s), 7.63 (1H, br s), 6.74 (1H, br d),4.27 (1H, m), 3.70 (1H, m), 2.83-2.60 (2H, m), 1.78-1.52 (7H, m), 1.35-1.07 (14H, m), 0.83 (2H, m).

Example 6 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-(cyclopropylmethyl)-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of cyclopropylmethylamine (522mg, 7.35mmol) in ethanol (2ml) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 10ml) then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (349mg) was then dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (120µl, 1.09mmol) and isobutyl chloroformate (140µl, 1.09mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (140µl, 1.15mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water

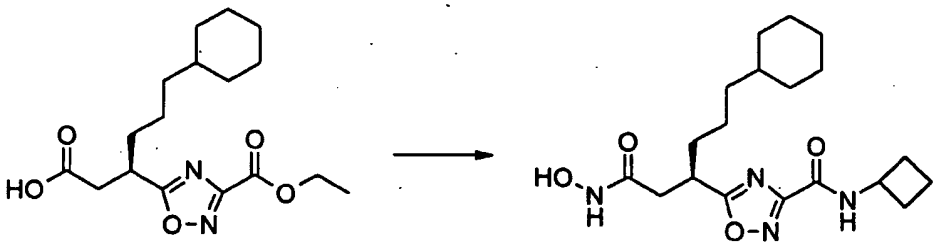
(5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by HPLC[a] to afford the title compound as a foam (88mg).

MS : 379 (MH^+), 401 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 9.20 (1H, br s), 7.05 (1H, br s), 3.72 (1H, m), 3.33 (2H, m), 2.87- 2.60 (2H, m), 1.88-1.52 (7H, m), 1.40-1.00 (8H, m), 0.83 (3H, m), 0.59 (2H, m), 0.30 (2H, m).

Example 7 :

N-Cyclobutyl-5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of cyclobutylamine (522mg, 7.35mmol) in ethanol (2ml) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 10ml) then extracted with ethyl acetate (x2). The organic layers were combined, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (462mg) was then dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (150µl, 1.36mmol)and isobutyl chloroformate (180µl, 1.39mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (190µl, 1.55mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water (5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by HPLC[a] to afford a residue (63mg) which was dissolved in dichloromethane (3ml), cooled to 0°C and treated sequentially with N-methylmorpholine (20µl, 0.18mmol)and isobutyl chloroformate (23µl, 0.18mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated

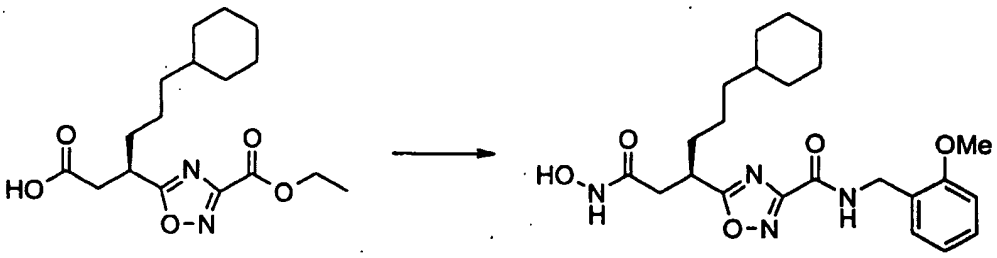
with O-(trimethylsilyl)hydroxylamine(24µl, 0.20mmol) and stirring continued for 3 hours. Further O-(trimethylsilyl)hydroxylamine(30µl, 0.25mmol) was added and stirring continued for 17 hours. The reaction was quenched with methanol and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was then dissolved in methanol (5ml), treated with potassium carbonate (110mg) and stirred at room temperature for 17 hours. The mixture was treated with a few drops of acetic acid and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a foam (24mg)

MS : 379 (MH^+), 401 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.80 (1H, br s), 7.06 (1H, br d), 4.57 (1H, m), 3.70 (1H, m), 2.85-2.54 (2H, m), 2.43 (1H, m), 2.05 (1H, m), 1.87-1.41 (11H, m), 1.38-0.98 (8H, m), 0.84 (2H, m).

Example 8 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-(2-methoxybenzyl)-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of 2-methoxybenzylamine (1.00g, 7.35mmol) in ethanol (2ml) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 10ml) then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (672mg) was then dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (180µl, 1.64mmol) and isobutyl chloroformate (210µl, 1.63mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-

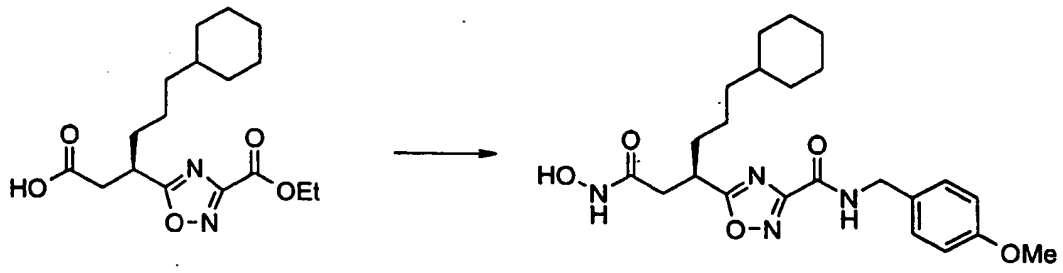
(trimethylsilyl)hydroxylamine (220µl, 1.80mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water (5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by HPLC[a] to afford the title compound as a foam (140mg).

MS : 445 (MH^+), 462 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 7.44 (1H, br s), 7.29 (2H, m), 6.91 (2H, m), 4.63 (2H, d, J=5Hz), 3.89 (3H, s), 3.71 (1H, m), 2.86-2.54 (2H, m), 1.90-1.48 (7H, m), 1.39-1.00 (8H, m), 0.83 (2H, m).

Example 9 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-(4-methoxybenzyl)-1,2,4-oxadiazole-3-carboxamide



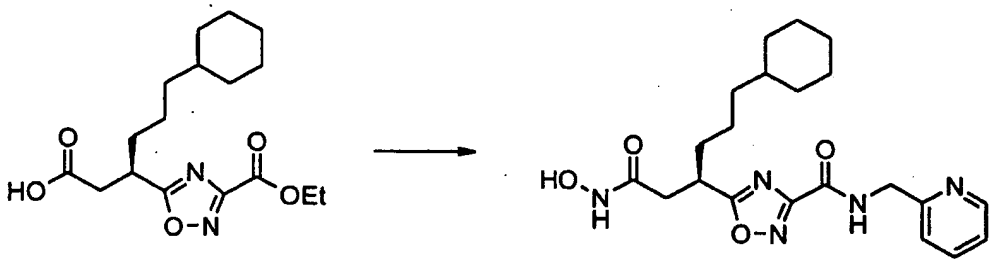
A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of 4-methoxybenzylamine (1.00g, 7.35mmol) in ethanol (2ml) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 10ml) then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (578mg) was then dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (160µl, 1.45mmol) and isobutyl chloroformate (190µl, 1.47mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (195µl, 1.60mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water (5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by HPLC[a] to afford the title compound as a foam (74mg).

MS : 445 (MH^+), 462 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 7.37 (2H, d, J=8Hz), 6.89 (2H, d, J=8Hz), 4.50 (2H, s), 3.76 (3H, s), 3.60 (1H, m), 2.73-2.50 (2H, m), 1.86-1.66 (7H, m), 1.40-1.09 (8H, m), 0.85 (2H, m).

Example 10 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-(2-pyridinylmethyl)-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (500mg, 1.47mmol) in ethanol (13ml) was treated with a solution of 2-aminomethylpyridine (794mg, 7.35mmol) in ethanol (2ml) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 10 hours. The solvent was removed under reduced pressure. The residue was dissolved in hydrochloric acid (1M, 10ml), neutralised to pH 4 with a saturated aqueous solution of ammonium hydroxide then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. This residue (467mg) was then dissolved in dichloromethane (15ml), cooled to 0°C and treated sequentially with N-methylmorpholine (140µl, 1.27mmol) and isobutyl chloroformate (165µl, 1.28mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (170µl, 1.39mmol) and stirring continued for 10 minutes at 0° then for 17 hours at room temperature. The mixture was then treated with trifluoroacetic acid : water (5ml, 9 : 1) and the solution stirred for 30 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by reverse phase HPLC[b] to afford a solid (130mg) which was dissolved in dichloromethane (5ml), cooled to 0°C and treated sequentially with N-methylmorpholine (33µl, 0.30mmol)and isobutyl chloroformate (38µl, 0.30mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine(40µl, 0.32mmol) and stirring continued for 3 hours. The reaction was quenched with methanol and the solvent removed under reduced pressure. The residue

was dissolved in ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was dissolved in methanol (5ml), treated with potassium carbonate (110mg, 0.80mmol) and stirred at room temperature for 17 hours. The mixture was treated with a few drops of acetic acid and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[a] to afford the title compound as a solid (34mg).

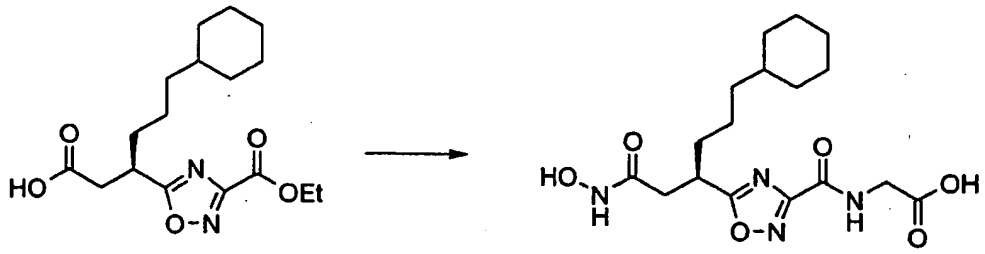
MPt.: 128-130°C

MS : 416 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.50 (2H, m), 7.72 (1H, dd, J= 7, 7Hz), 7.40-7.18 (2H, m), 4.74 (2H, d, J=5Hz), 3.67 (1H, m), 2.83-2.50 (2H, m), 1.86-1.42 (7H, m), 1.40-0.97 (8H, m), 0.80 (2H, m).

Example 11 :

2-{[(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]amino}acetic acid



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (527mg, 1.56mmol) in ethanol (20ml) was treated with triethylamine (508mg, 5.02mmol) and glycine t-butyl ester hydrochloride (743mg, 4.43mmol) and the resulting solution was heated at 80°C under a nitrogen atmosphere for 30 hours. The solvent was removed under reduced pressure and the residue was dissolved in hydrochloric acid (1M, 20ml) then extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (1 : 1) then dichloromethane : methanol (19 : 1). This residue (430mg, 1.02mmol) was dissolved in dichloromethane (10ml), cooled to 0°C and treated sequentially with N-methylmorpholine (130µl,

1.20mmol) and isobutyl chloroformate (150µl, 1.20mmol). This mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour, then treated with O-(trimethylsilyl)hydroxylamine (160µl, 1.30mmol). The mixture was stirred for 17 hours being allowed to warm to room temperature over this time. The mixture was diluted with dichloromethane, washed with aqueous citric acid solution (10% w/v), dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (10ml), treated with trifluoroacetic acid (10ml) and the solution was stirred for 2.5 hours at room temperature. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was purified by HPLC[b] to afford the title compound as a white solid (350mg).

MPt.: 141-142°C

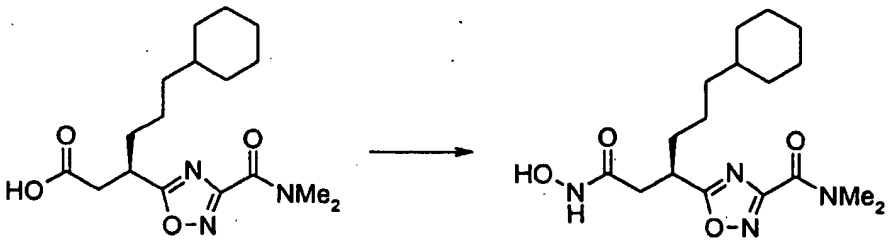
MS : 383 (MH^+), 405 (MNa^+)

Analysis : Found C, 50.80; H, 7.00; N, 13.90%; $C_{17}H_{26}N_4O_6.H_2O$ requires C, 50.99; H, 7.05; N, 13.99%

^{1}H-NMR (CD_3OD) δ : 4.10 (2H, s), 3.63 (1H, m), 2.72-2.51 (2H, m), 1.85-1.60 (7H, m), 1.38-1.10 (8H, m), 0.86 (2H, m).

Example 12 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N,N-dimethyl-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-{3-[(dimethylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 11) (60mg, 0.18mmol) and N,N-diisopropylethylamine (30µl, 0.18mmol) in N-N-dimethylformamide (3ml) was treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (100mg, 0.27mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour. Further N,N-diisopropylethylamine (90µl, 0.52mmol) was then added, followed by hydroxylamine

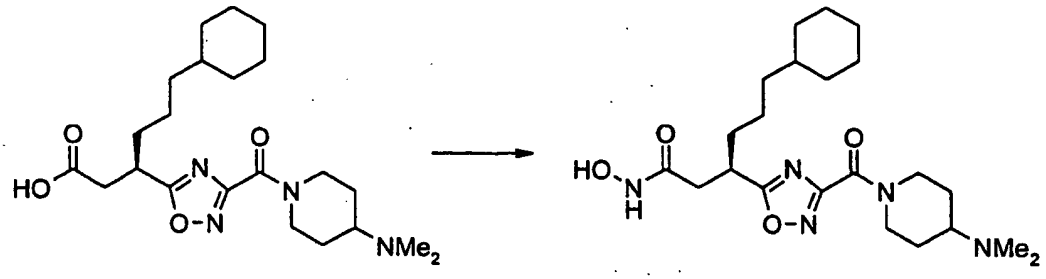
hydrochloride (35mg, 0.52mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was partitioned between ethyl acetate and pH 7 aqueous buffer. The layers were separated and the aqueous phase extracted with ethyl acetate (x2). The combined organic layers were washed sequentially with aqueous citric acid solution (5% w/v) and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (90 : 10) gradually changing to dichloromethane : ethyl acetate (50 : 50) then to dichloromethane : methanol (95 : 5). The residue was further purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (95 : 5) to afford the title compound as an oil which crystallised on standing (35mg).

MS : 353 (MH^+)

^{1}H-NMR (DMSO-d_6) δ : 10.50 (1H, br s), 8.81 (1H, br s), 3.48 (1H, m), 3.03 (3H, s), 2.93 (3H, s), 2.50 (2H, m), 1.76-1.52 (7H, m), 1.32-1.03 (8H, m), 0.80 (2H, m).

Example 13 :

(3R)-6-Cyclohexyl-3-(3-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)-N-hydroxyhexanamide



A solution of (3R)-6-cyclohexyl-3-(3-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid trifluoroacetate (Preparation 26) (702mg, 1.31mmol) and N-methylmorpholine (159µl, 1.45mmol) in N,N-dimethylformamide (15ml) was cooled to 0°C and then treated with dropwise with isobutyl chloroformate (188µl, 1.45mmol). The resulting solution was stirred at 0°C under a nitrogen atmosphere for 45 minutes. Hydroxylamine hydrochloride (274mg, 3.94mmol) was then added followed by further N-methylmorpholine (433µl, 3.94mmol) and the mixture was stirred for 18 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue was dissolved in a saturated aqueous solution of sodium carbonate. The pH of the solution was adjusted to 9 by dropwise addition of acetic

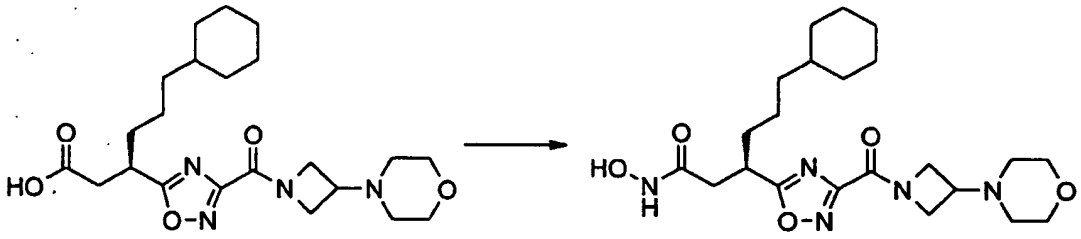
acid and the product was then extracted with ethyl acetate (x2). The combined organic phases were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : 0.88 ammonia (90 : 10 : 1) then dichloromethane : methanol : 0.88 ammonia (80 : 20 : 2) to afford the title compound as an oil (23mg)

MS : 436 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.68 (1H, m), 3.95 (1H, m), 3.48 (1H, m), 3.18 (1H, m), 2.91 (1H, m), 2.72-2.54 (3H, m), 2.36 (6H, s), 2.04 (1H, m), 1.96 (1H, m), 1.84-1.60 (7H, m), 1.50 (2H, m), 1.35-1.10 (8H, m), 0.88 (2H, m).

Example 14 :

(3R)-6-Cyclohexyl-N-hydroxy-3-(3-{[3-(4-morpholinyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanamide



A solution of (3R)-6-cyclohexyl-3-(3-{[3-(4-morpholinyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid trifluoroacetate (Preparation 28) (1173mg, 2.70mmol) and N-methylmorpholine (327µl, 2.97mmol) in N,N-dimethylformamide (25ml) was cooled to 0°C, treated dropwise with isobutyl chloroformate (386µl, 2.97mmol) and stirred under a nitrogen atmosphere at 0°C for 45 minutes. Hydroxylamine hydrochloride (564mg, 8.11mmol) was then added followed by further N-methylmorpholine (891µl, 8.11mmol) and the mixture was stirred for 18 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue dissolved in a saturated aqueous solution of sodium carbonate. The pH of the solution was adjusted to 9 by dropwise addition of acetic acid. Water was added (75ml) and the product was then extracted with ethyl acetate (x2). The combined organic phases were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : 0.88 ammonia (90 : 10 : 1) then

dichloromethane : methanol : 0.88 ammonia (80 : 20 : 2) . The product was further purified by HPLC to afford the title compound as a white solid (151mg)

MS : 450 (MH^+)

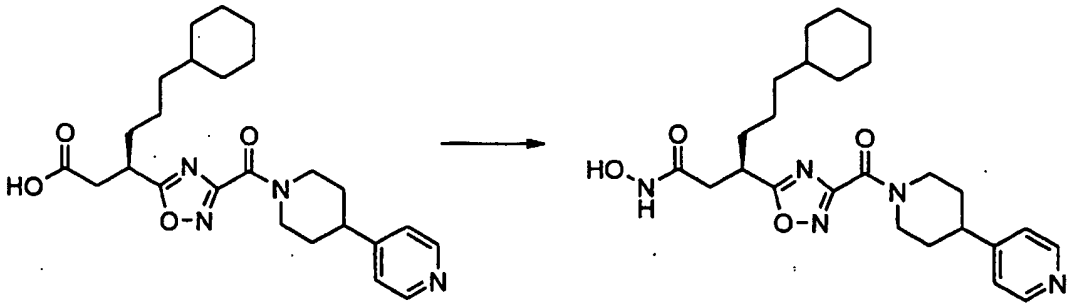
Analysis : Found C, 56.19; H, 7.61; N, 14.81%; $C_{22}H_{35}N_5O_5.H_2O$ requires C, 56.51; H, 7.96; N, 14.98%

^{1}H-NMR (CD_3OD) δ : 4.63 (1H, m), 4.42 (1H, m), 4.44 (1H, m), 4.03 (1H, m), 3.75 (4H, m), 3.41 (1H, m), 3.30 (1H, m), 2.72-2.53 (2H, m), 2.45 (4H, m), 1.83-1.56 (7H, m), 1.36-1.07 (8H, m), 0.87 (2H, m).

MPt. : 52-63°C

Example 15 :

(3R)-6-Cyclohexyl-N-hydroxy-3-(3-{[4-(4-pyridinyl)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanamide



A solution of (3R)-6-cyclohexyl-3-(3-{[4-(4-pyridinyl)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 32) (311mg, 0.68mmol) and N-methylmorpholine (83µl, 0.75mmol) in N,N-dimethylformamide (15ml) was cooled to 0°C, treated dropwise with isobutyl chloroformate (98µl, 0.75mmol) and the resulting solution was stirred at 0°C for 45 minutes. Hydroxylamine hydrochloride (142mg, 2.05mmol) was then added followed by further N-methylmorpholine (226µl, 2.05mmol) and the mixture was stirred for 18 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (50ml) and water (50ml). The layers were separated and the aqueous phase extracted with ethyl acetate (x2). The combined organic phases were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC to afford a residue that

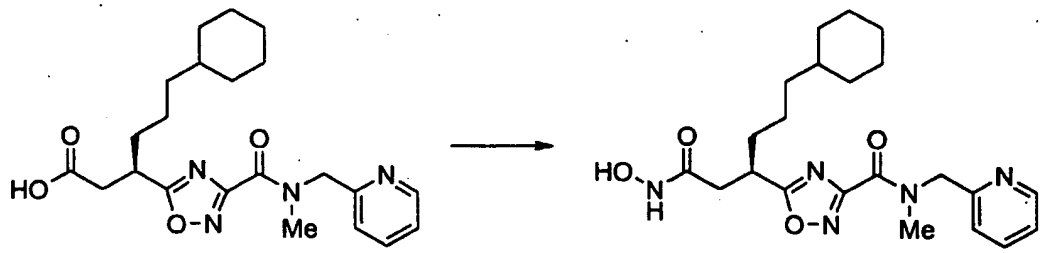
was partitioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was triturated with diethyl ether to yield the title compound as a white solid (94mg).

MS : 470 (MH^+)

^{1}H-NMR (CD_3OD) δ : 8.45 (2H, d, J=4Hz), 7.37 (2H, d, J=4Hz), 4.79 (1H, m), 4.00 (1H, m), 3.60 (1H, m), 3.32 (1H, m), 3.00 (2H, m), 2.70-2.52 (2H, m), 2.06-1.85 (2H, m), 1.83-1.60 (9H, m), 1.39-1.12 (8H, m), 0.86 (2H, m).

Example 16 :

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-methyl-N-(2-pyridinylmethyl)-1,2,4-oxadiazole-3-carboxamide



A solution of (3R)-6-cyclohexyl-3-(3-{[methyl(2-pyridinylmethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 36) (453mg, 1.09mmol)and N-methylmorpholine (132µl, 1.20mmol) in anhydrous tetrahydrofuran (10ml) was cooled to 0°C, treated with isobutyl chloroformate (155µl, 1.20mmol) and stirred under a nitrogen atmosphere for 2 hours. O-(trimethylsilyl)hydroxylamine (160µl, 1.31mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with saturated aqueous ammonium chloride solution (10ml) and stirred for 1 hour. This mixture was then diluted with water and extracted with ethyl acetate (x3). The combined organic layers were sequentially washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate : isopropanol (95 : 5) then a gradient system of dichloromethane : methanol (90 : 10) to dichloromethane : methanol (80 : 20) to afford a residue (260mg, 0.31mmol) which was dissolved in methanol (5ml) and treated with potassium carbonate (138mg, 1.00mmol) and the mixture was stirred at room temperature for 17 hours. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and a saturated aqueous solution of ammonium chloride. The layers were separated

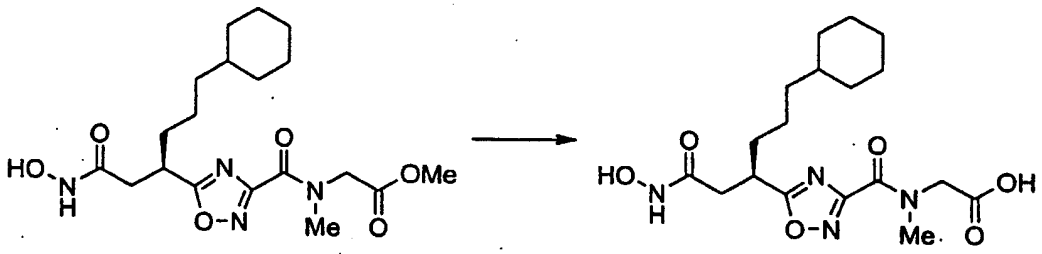
and the aqueous layer was extracted with ethyl acetate (x4). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[a] to afford the title compound as a white solid (84mg)

MS : 430 (MH^+)

^{1}H-NMR ($CDCl_3$) (mixture of rotamers) δ : 8.55 (1H, m), 7.72 (1H, m), 7.42-7.20 (2H, m), 4.84 (2H, m), 3.64 (1H, m), 3.24 (1.2H, s), 3.18 (1.8H, s), 2.84-2.53 (2H, m), 1.86-1.45 (7H, m), 1.39-0.88 (8H, m), 0.80 (2H, m).

Example 17 :

2-[[(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl](methyl)amino]acetic acid



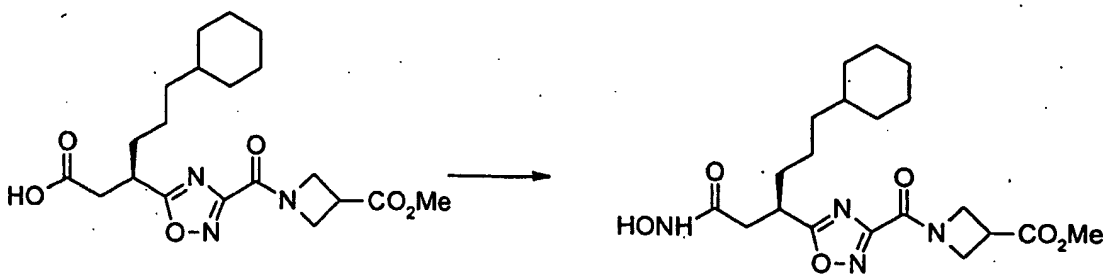
A solution of methyl 2-[[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl](methyl)amino]acetate (Preparation 40) (180mg, 0.44mmol) in 1,4-dioxane (4ml) was cooled to 0°C and treated with lithium hydroxide monohydrate (42mg, 1mmol). The mixture was stirred for 1 hour being allowed to warm to room temperature over this time. The mixture was then treated with hydrochloric acid (2M), diluted with water and extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[b] to afford the title compound as a white foam (95mg).

MS : 397(MH^+), 419 (MNa^+)

^{1}H-NMR (CD_3OD) (mixture of rotamers) δ : 4.39 (1H, s), 4.27 (1H, s), 3.60 (1H, m), 3.23 (1.5H, s), 3.16 (1.5H, s), 2.73-2.50 (2H, m), 1.86-1.58 (7H, m), 1.39-1.08 (8H, m), 0.87 (2H, m).

Example 18 :

Methyl 1-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylate



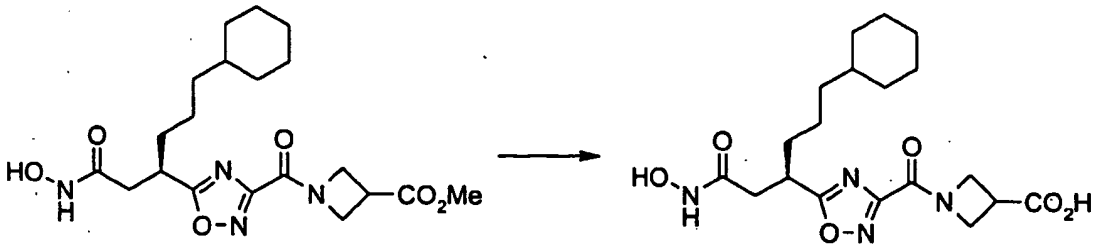
A solution of (3R)-6-cyclohexyl-3-(3-{[3-(methoxycarbonyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 43) (200mg, 0.49mmol) and N-methylmorpholine (59µl, 0.54mmol) in anhydrous dichloromethane (7ml) was cooled to 0°C, treated with isobutyl chloroformate (70µl, 0.54mmol) and stirred under a nitrogen atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (175µl, 1.47mmol) was added and the mixture was for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with aqueous citric acid solution (10% w/v, 10ml) and stirred for 2 hours. This mixture was then diluted with water and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC to afford the title compound as a foam (150mg).

MS : 423 (MH^+), 440 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 4.80-4.62 (2H, m), 4.46-4.25 (2H, m), 3.77 (3H, s), 3.63 (2H, m), 2.75-2.50 (2H, m), 1.83-1.57 (7H, m), 1.39-1.08 (8H, m), 0.86 (2H, m).

Example 19 :

1-[(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylic acid



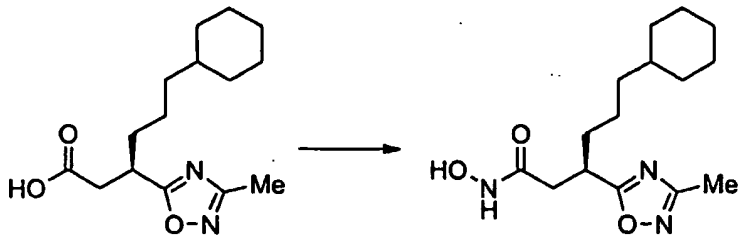
A solution of methyl 1-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylate (Example 18) (130mg, 0.31mmol) in 1,4-dioxane (3ml) was cooled to 0°C and treated with lithium hydroxide monohydrate (25mg, 0.60mmol). The mixture was stirred for 1 hour being allowed to warm to room temperature over this time. Further lithium hydroxide monohydrate (25mg, 0.60mmol) was added and the mixture stirred for 3 hours. The mixture was then treated with hydrochloric acid (2M), diluted with water and extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[b] to afford the title compound as a foam (110mg).

MS : 409 (MH^+), 431 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : nmr - needs redoing 4.71 (2H, m), 4.35 (2H, m), 3.69-3.43 (2H, m), 2.86-2.56 (2H, m), 1.90-1.52 (7H, m), 1.40-0.99 (8H, m), 0.83 (2H, m).

Example 20 :

(3R)-6-Cyclohexyl-N-hydroxy-3-(3-methyl-1,2,4-oxadiazol-5-yl)hexanamide



A solution of (3R)-6-cyclohexyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 45) (170mg, 0.61mmol) in anhydrous tetrahydrofuran (2ml) was treated with 1,1'-carbonyldiimidazole (98mg, 0.61mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 20 minutes. Hydroxylamine hydrochloride (42mg, 0.61mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure

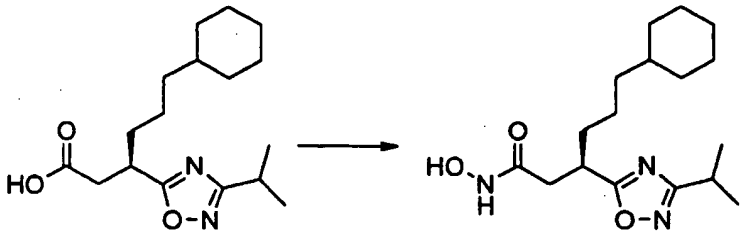
and the residue partitioned between hydrochloric acid (0.5M) and ethyl acetate. The layers were separated and the organic phase was washed with water, dried over anhydrous sodium sulphate, filtered and solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (98 : 2) to afford the title compound as an oil (82mg).

MS : 296 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.56 (1H, m), 2.70 (1H, m), 2.58 (1H, m), 2.38 (3H, s), 1.88-1.42 (7H, m), 1.39-1.03 (8H, m), 0.83 (2H, m)

Example 21 :

(3R)-6-Cyclohexyl-N-hydroxy-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)hexanamide



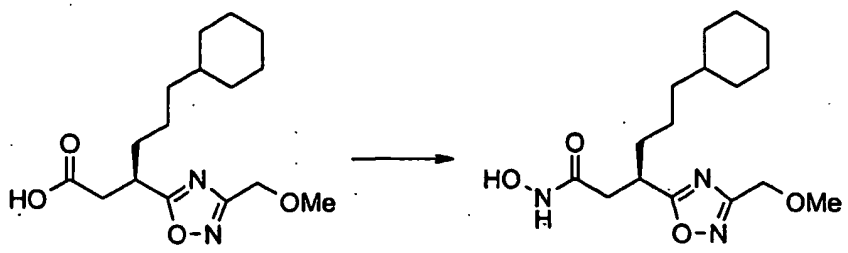
A solution of (3R)-6-cyclohexyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 47) (175mg, 0.57mmol) in anhydrous tetrahydrofuran (10ml) was treated with 1,1'-carbonyldiimidazole (93mg, 0.57mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 1 hour. Hydroxylamine hydrochloride (40mg, 0.57mmol) was then added and the mixture stirred for 18 hours. The mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as an oil (44mg).

MS : 324 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.54 (1H, m), 3.06 (1H, m), 2.75-2.48 (2H, m), 1.88-1.58 (7H, m), 1.39-1.05 (14H, m), 0.83 (2H, m)

Example 22:

(3R)-6-Cyclohexyl-N-hydroxy-3-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]hexanamide



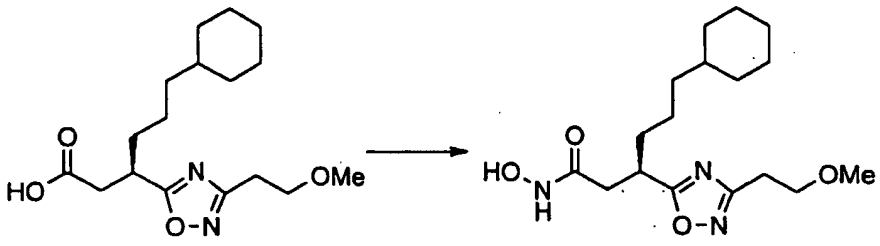
A solution of (3R)-6-cyclohexyl-3-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 49) (250mg, 0.81mmol) in anhydrous tetrahydrofuran (10ml) was treated with 1,1'-carbonyldiimidazole (130mg, 0.81mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. Hydroxylamine hydrochloride (56mg, 0.81mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as an oil (75mg).

MS : 326 (MH^+), 348 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.57 (2H, s), 3.62 (1H, m), 3.46 (3H, s), 2.80-2.52 (2H, m), 1.88-1.42 (7H, m), 1.39-1.03 (8H, m), 0.83 (2H, m)

Example 23:

(3R)-6-Cyclohexyl-N-hydroxy-3-[3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl]hexanamide



A solution of ((3R)-6-cyclohexyl-3-[3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 51) (245mg, 0.76mmol) in anhydrous tetrahydrofuran (10ml) was treated with 1,1'-carbonyldiimidazole (123mg, 0.76mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 1 hour. Hydroxylamine hydrochloride (53mg, 0.76mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure

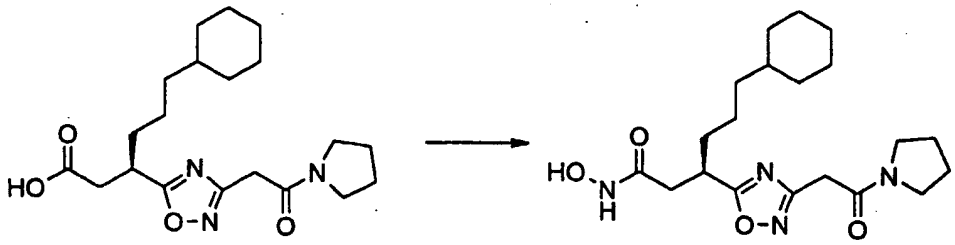
and the residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5). The residue was dissolved in ethyl acetate, washed with hydrochloric acid (1M), dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil (100mg)

MS : 340 (MH^+), 362 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 3.77 (2H, m), 3.55 (1H, m), 3.36 (3H, s), 3.00 (2H, t, J=6Hz), 2.80-2.52 (2H, m), 1.88-1.52 (7H, m), 1.39-1.05 (8H, m), 0.83 (2H, m)

Example 24:

(3R)-6-Cyclohexyl-N-hydroxy-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}hexanamide

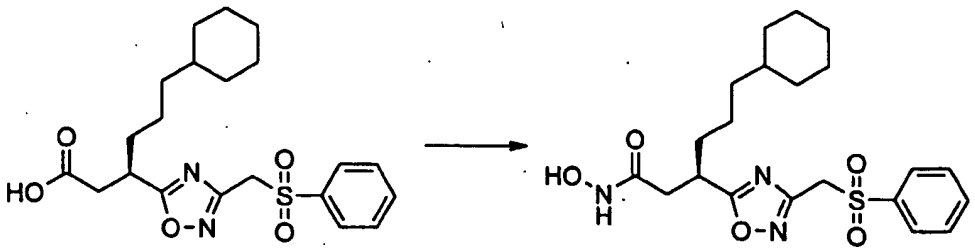


A solution of (3R)-6-cyclohexyl-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 53) (200mg, 0.53mmol) in anhydrous tetrahydrofuran (10ml) was treated with 1,1'-carbonyldiimidazole (86mg, 0.53mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. Hydroxylamine hydrochloride (37mg, 0.53mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (90 : 10 : 1) to afford the title compound as a colourless oil (50mg).

^{1}H-NMR ($CDCl_3$) δ : 3.80 (2H, m), 3.67-3.40 (5H, m), 2.80-2.52 (2H, m), 2.13-0.98 (19H, m), 0.83 (2H, m)

Example 25 :

(3R)-6-Cyclohexyl-N-hydroxy-3-{3-[(phenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanamide



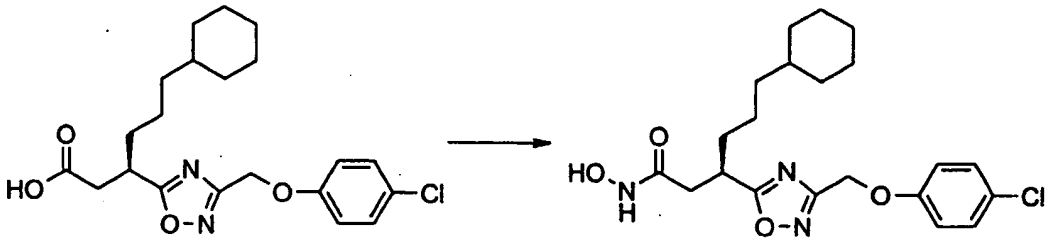
A solution of (3R)-6-cyclohexyl-3-{3-[(phenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 55) (60mg, 0.14mmol) in anhydrous tetrahydrofuran (4ml) was treated with 1,1'-carbonyldiimidazole (25mg, 0.15mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. Hydroxylamine hydrochloride (10mg, 0.14mmol) was then added and the mixture was stirred for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as an oil (15mg).

MS : 436 (MH^+), 453 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 8.93 (1H, br s), 8.01-7.40 (5H, m), 4.53 (2H, s), 3.60 (1H, m), 2.85-2.52 (2H, m), 1.84-1.43 (7H, m), 1.39-1.00 (8H, m), 0.85 (2H, m)

Example 26 :

(3R)-3-{3-[(4-Chlorophenoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexyl-N-hydroxyhexanamide



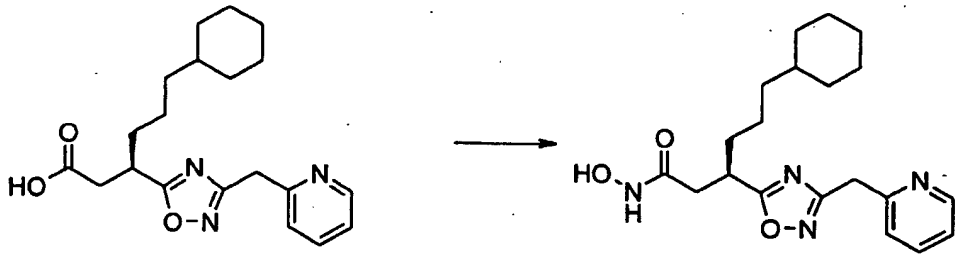
A solution of (3R)-3-{3-[(4-chlorophenoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid (Preparation 57) (180mg, 0.44mmol) in anhydrous tetrahydrofuran (10ml) was treated with 1,1'-carbonyldiimidazole (71mg, 0.44mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. Hydroxylamine hydrochloride (30mg, 0.44mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated

and the organic phase was washed with brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as a glass (53mg).

^{1}H-NMR ($CDCl_3$) δ : 7.24 (2H, m), 6.94 (2H, d, J=8Hz), 5.13 (2H, s), 3.70-3.44 (1H, m), 3.00-2.50 (2H, m), 1.85-1.53 (7H, m), 1.37-1.02 (8H, m), 0.82 (2H, m)

Example 27 :

(3R)-6-Cyclohexyl-N-hydroxy-3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanamide



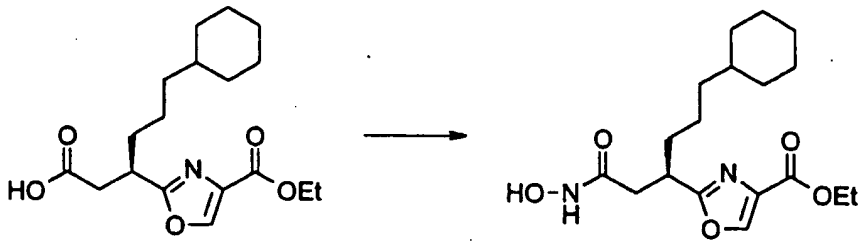
A solution of (3R)-6-cyclohexyl-3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid trifluoroacetate (Preparation 59) (214mg, 0.45mmol) in anhydrous tetrahydrofuran (5ml) was treated with 1,1'-carbonyldiimidazole (194mg, 1.20mmol) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 hours. Hydroxylamine hydrochloride (83mg, 1.20mmol) was then added and the mixture stirred for 18 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water then brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as a colourless oil (120mg).

MS : 373 (MH^+), 395 (MNa^+)

^{1}H-NMR (DMSO-d_6) δ : 8.79 (1H, br s), 8.45 (1H, d, J=5Hz), 7.74 (1H, t, J=5Hz), 7.38-7.20 (2H, m), 4.20 (2H, s), 3.40 (1H, m), 2.48-2.31 (2H, m), 1.89-1.43 (7H, m), 1.29-0.95 (8H, m), 0.76 (2H, m)

Example 28:

Ethyl 2-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,3-oxazole-4-carboxylate



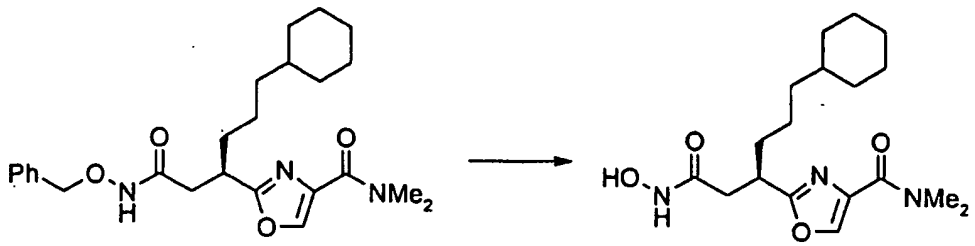
A solution of (3R)-6-cyclohexyl-3-[4-(ethoxycarbonyl)-1,3-oxazol-2-yl]hexanoic acid (Preparation 63) (130mg, 0.39mmol) and N,N-diisopropylethylamine (67µl, 0.39mmol) in N,N-dimethylformamide (6ml) was treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (220mg, 0.58mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 45 minutes. Further N,N-diisopropylethylamine (270µl, 1.54mmol) was then added, followed by hydroxylamine hydrochloride (80mg, 1.16mmol) and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and pH 7 aqueous buffer. The organic layer was separated, washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (98 : 2) to afford the title compound (20mg).

MS : 353 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.14 (1H, s), 4.37 (2H, q, J=7Hz), 3.50 (1H, m), 2.76 (1H, m), 2.57 (1H, m), 1.88-1.52 (7H, m), 1.37 (3H, t, J=7Hz), 1.32-1.02 (8H, m), 0.83 (2H, m).

Example 29:

2-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N,N-dimethyl-1,3-oxazole-4-carboxamide



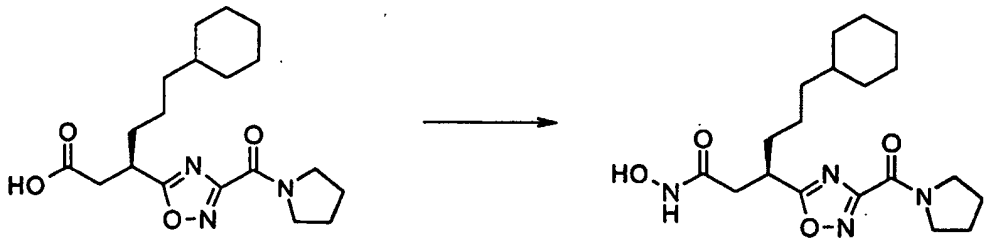
A solution of 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N,N-dimethyl-1,3-oxazole-4-carboxamide (Preparation 66) (100mg, 0.23mmol) in ethanol (5ml) was treated with 5% palladium on barium sulphate (50mg), pressurised to 1 atm with hydrogen in a sealed vessel and the mixture was stirred at room temperature for 2 hours. The solution was filtered through Arbocel® and the solvent removed from the filtrate under reduced pressure. The residue was azeotroped from dichloromethane (x3) then dichloromethane : ether (1ml : 4ml) to afford the title compound as a foam (75mg).

MS : 351 (M^+)

^{1}H-NMR ($CDCl_3$) δ : 7.94 (1H, s), 3.52 (1H, m), 3.38-2.94 (6H, br d), 2.73-2.45 (2H, m), 1.85-1.47 (7H, m), 1.41-0.98 (8H, m), 0.83 (2H, m).

Example 30 :

(3R)-6-Cyclohexyl-N-hydroxy-3-[3-(1-pyrrolidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanamide

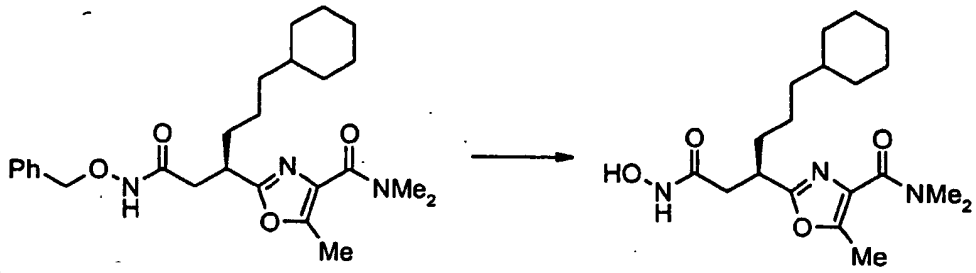


A solution of (3R)-6-cyclohexyl-3-[3-(1-pyrrolidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 13) (288mg, 0.79mmol) and N,N-diisopropylethylamine (138µl, 0.79mmol) in N,N-dimethylformamide (6ml) was treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (452mg, 1.19mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour. Further N,N-diisopropylethylamine (552µl, 3.16mmol) was then added, followed by the hydroxylamine hydrochloride (165mg, 2.38mmol) and the mixture stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue wasa partitioned between ethyl acetate and pH 7 aqueous buffer. The organic layer was separated, washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (98 : 2) to afford the title compound as a foam (126mg).
MS : 379 (MH^+), 396 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 3.75 (2H, m), 3.60 (3H, m), 2.66 (1H, dd, J=13, 8Hz), 2.57 (1H, dd, J=13, 3Hz), 1.98 (4H, m), 1.86-1.58 (7H, m), 1.40-1.07 (8H, m), 0.87 (2H, m).

Example 31:

2-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N,N,5-trimethyl-1,3-oxazole-4-carboxamide



A solution of 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N,N,5-trimethyl-1,3-oxazole-4-carboxamide (Preparation 73) (105mg, 0.23mmol) in ethanol (5ml) was treated with 5% palladium on barium sulphate (45mg) and ammonium formate (73mg, 1.15mmol) and the mixture was heated at 45°C for 17 hours. Further palladium on barium sulphate (30mg) and ammonium formate (60mg, mmol) were added and the heating was continued for 2 hours. The solution was filtered through Arbocel® and the solvent removed from the filtrate under reduced pressure. The residue was azeotroped from dichloromethane (x3) then purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (98:2:0.2 to 90:10:1) to afford the title compound as a foam (25mg).

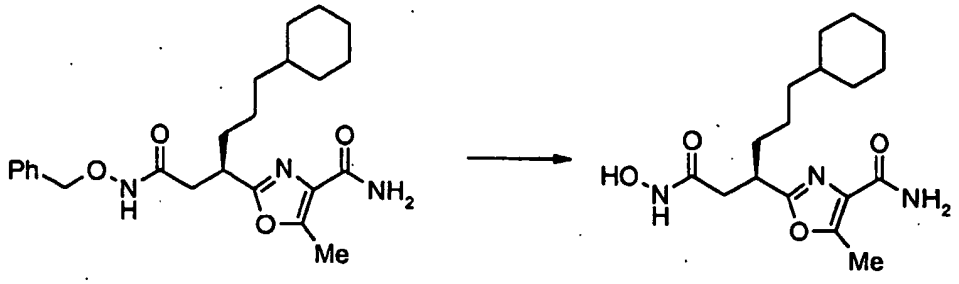
MS : 366(MH^+), 388 (MNa^+)

Analysis: Found C, 61.77; H, 8.62; N, 11.22%; $C_{19}H_{31}N_3O_4 .0.1H_2O$ requires C, 62.14; H, 8.56; N, 11.44%

^{1}H-NMR (CD_3) δ : 10.37 (1H, br s), 8.66 (1H, br s), 3.25 (1H, m), 3.14 (3H, br s), 2.91 (3H, br s), 2.43-2.21 (5H, m), 1.66-1.50 (7H, m), 1.24-1.00 (8H, m), 0.79 (2H, m).

Example 32:

2-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-5-methyl-1,3-oxazole-4-carboxamide



A solution of 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxamide (Preparation 74) (133mg, 0.31mmol) in ethanol (6ml) was treated with 5% palladium on barium sulphate (80mg) and ammonium formate (196mg, 3.10mmol) and the mixture was heated at 45°C for 2.5 hours. The solution was filtered through Arbocel® and the solvent removed from the filtrate under reduced pressure. The residue was azeotroped from dichloromethane (x3) then purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (98:2:0.2 to 90:10:1) to afford the title compound as a white solid (56mg).

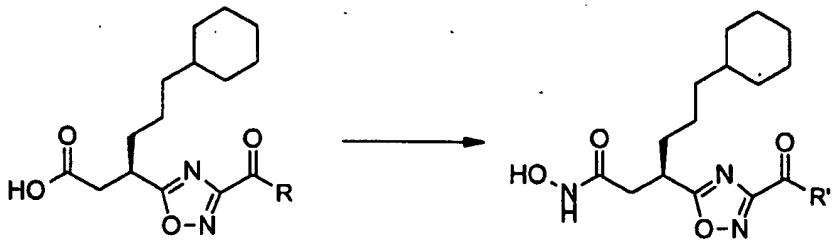
MS : 338 (MH^+), 360 (MNa^+)

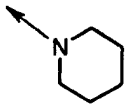
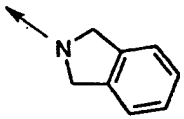
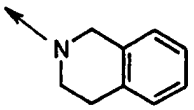
Analysis: Found C, 61.77; H, 8.62; N, 11.22%; $C_{19}H_{31}N_3O_4 .0.1H_2O$ requires C, 62.14; H, 8.56; N, 11.44%

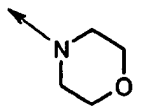
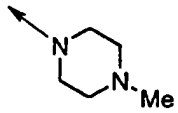
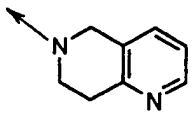
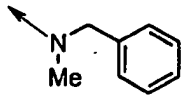
^{1}H-NMR (DMSO-d_6) δ : 7.12 (2H, br s), 3.52 (1H, m), 2.56-2.21 (2H, m), 1.67-1.49 (7H, m), 1.23-1.00 (8H, m), 0.79 (2H, m).

Other compounds prepared by the same general method, using appropriate starting materials (see Preparations section below), are listed in Table 1 below.

Table 1

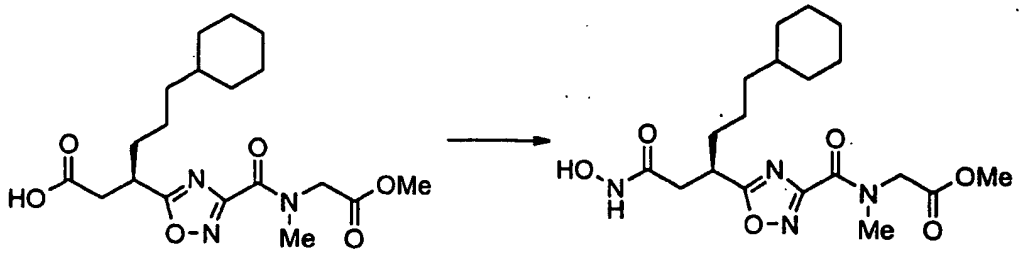


Example	R'	Elemental Analysis	LRMS	^{1}H, δ
33	$NHCH_2Ph$	Found C, 62.93; H, 7.37; N, 13.29%; $C_{22}H_{30}N_4O_4$. $0.25H_2O$ requires C, 63.06, H, 7.34; N, 13.37%	415 (MH^+) 432 (MNH_4^+)	(CD_3OD) : 7.40-7.21 (5H, m), 4.57 (2H, s), 3.60 (1H, m), 2.72-2.53 (2H, m), 1.86-1.59 (7H, m), 1.40-1.10 (8H, m), 0.86 (2H, m)
34			393 (MH^+) 410 (MNH_4^+)	(CD_3OD) : 3.73 (2H, m), 3.60 (1H, m), 3.47 (2H, m), 2.73-2.50 (2H, m), 1.91-1.53 (13H, m), 1.43-1.05 (8H, m), 0.86 (2H, m).
35			428 ($M2H^+$)	(CD_3OD) : 7.42-7.27 (4H, m), 5.20 (2H, s), 4.98 (2H, s), 3.64 (1H, m), 2.70 (1H, dd, J=13, 8Hz), 2.50 (1H, dd, J=13, 4Hz), 1.89-1.58 (7H, m), 1.40-1.10 (8H, m), 0.88 (2H, m).
36		Found C, 64.53; H, 7.43; N, 12.58%; $C_{24}H_{32}N_4O_4$. $0.25H_2O$ requires C, 64.77, H, 7.36; N, 12.59%	441 (MH^+), 463 (MNa^+)	(CD_3OD) : (mixture of rotamers) 7.32-7.04 (4H, m), 4.83 (1.2H, s), 4.73 (0.8H, s), 4.00 (0.8H, m), 3.83 (1.2H, m), 3.64 (1H, m), 3.00 (2H, m), 2.77-2.54 (2H, m), 1.90-1.53 (7H, m), 1.44-1.02 (8H, m), 0.88 (2H, m)

37			395 (MH^+), 412 (MNH_4^+)	(CD_3OD) : 3.75 (4H, m), 3.71-3.53 (5H, m), 2.62 (2H, m), 1.87-1.58 (7H, m), 1.40-1.06 (8H, m), 0.86 (2H, m)
38			408 (MH^+)	(CD_3OD) : 3.80 (2H, m), 2.60 (3H, m), 2.72-2.43 (6H, m), 2.33 (3H, s), 1.82-1.58 (7H, m), 1.40-1.09 (8H, m), 0.87 (2H, m)
39			442 (MH^+)	(CD_3OD) : (mixture of rotamers[1:2]) 8.39 (1H, m), 7.73 (0.67H, d, J=7Hz), 7.62 (0.33H, d, J=7Hz), 7.32 (1H, m), 4.94 (1.34H, m), 4.85 (0.66H, m), 4.12 (0.66H, t, J=4Hz), 3.95 (1.34H, t, J=4Hz), 3.63 (1H, m), 3.10 (2H, t, J=4Hz), 2.75-2.54 (2H, m), 1.86-1.59 (7H, m), 1.40-1.07 (8H, m), 0.89 (2H, m)
40			429 (MH+)	(CD_3OD) (mixture of rotamers[1:1]) 7.40-7.23 (5H, m), 4.80 (1H, s), 4.64 (1H, s), 3.62 (1H, m), 3.03 (1.5H, s), 2.99 (1.5H, s), 2.72-2.51 (2H, m), 1.86-1.55 (7H, m), 1.38-1.03 (8H, m), 0.84 (2H, m).

Example 41/ Preparation 40:

Methyl 2-[[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl](methyl)amino]acetate



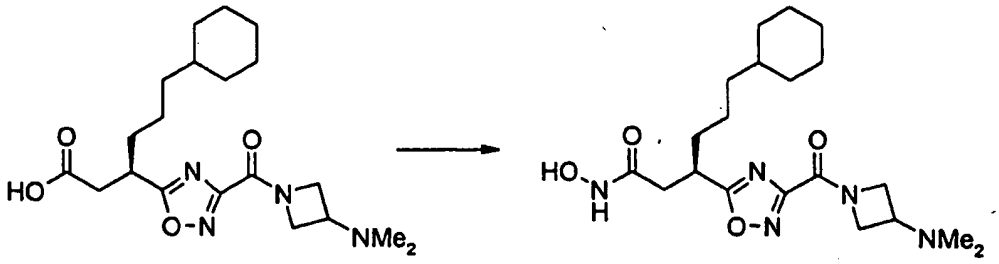
A solution of (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 39) (273mg, 0.70mmol)and N-methylmorpholine (85µl, 0.77mmol) in anhydrous dichloromethane (10ml) was cooled to 0°C, treated with isobutyl chloroformate (100µl, 0.77mmol) and the resulting mixture was stirred under a nitrogen atmosphere for 30 minutes. O-(Trimethylsilyl)hydroxylamine (250µl, 2.10mmol) was then added and the mixture stirred under a nitrogen atmosphere for 1 hour, being allowed to warm to room temperature over this time. The mixture was then quenched with methanol (10ml) and stirred for 10 minutes. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The layers were separated and the organic layer was sequentially washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[a] to afford the title compound as a colourless oil (187mg).

MS : 411 (MH^+), 433 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 4.50-4.21 (2H, m), 3.84-3.60 (4H, m), 3.32 (1.8H, s), 3.21 (1.2H, s), 2.81-2.56 (2H, m), 1.90-1.50 (7H, m), 1.40-1.03 (8H, m), 0.82 (2H, m).

EXAMPLE 42:

(3R)-6-Cyclohexyl-3-(3-{[3-(dimethylamino)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)-N-hydroxyhexanamide



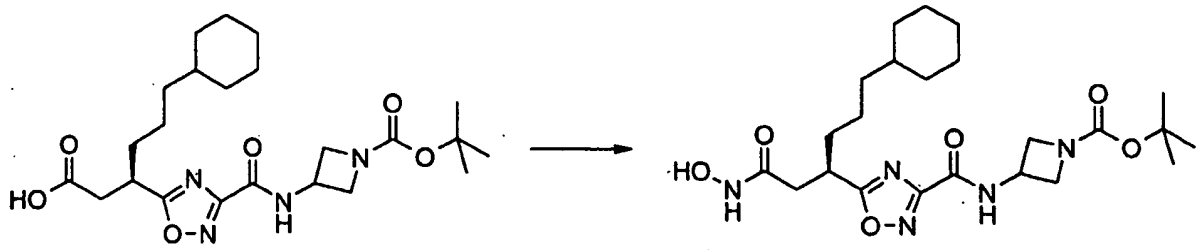
A solution of (3R)-6-cyclohexyl-3-(3-{[3-(dimethylamino)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 76) (200mg, 0.51mmol) and N-methylmorpholine (112µl, 1.00mmol) in anhydrous tetrahydrofuran (15ml) was cooled to 0°C, treated with isobutyl chloroformate (79µl, 0.69mmol) and stirred under a nitrogen atmosphere for 2 hours. O-(Trimethylsilyl)hydroxylamine (85µl, 0.61mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (2x25ml) and brine (25ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a foam (180mg).

MS : 408 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.60 (1H, m), 4.38 (1H, m), 4.22 (1H, m), 3.99 (1H, m), 3.60 (1H, m), 3.24 (1H, m), 2.64 (1H, dd), 2.57 (1H, dd), 2.20 (6H, s), 1.58-1.80 (6H, m), 1.08-1.36 (7H, m), 0.85 (2H, m).

Example 43:

tert-Butyl 3-{[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]amino}-1-azetidinecarboxylate



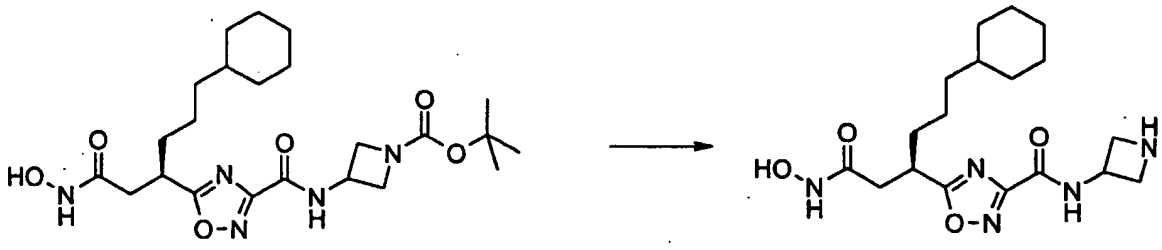
A solution of (3R)-3-[3-({[1-(tert-butoxycarbonyl)-3-azetidinyl]amino}carbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid (Preparation 79) (350mg, 0.75mmol) and N-methylmorpholine (163µl, 1.48mmol) in anhydrous tetrahydrofuran (15ml) was cooled to 0°C, treated with isobutyl chloroformate (116µl, 0.89mmol) and stirred under a nitrogen atmosphere for 2 hours. O-(Trimethylsilyl)hydroxylamine (272µl, 2.22mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (2x25ml) and brine (25ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of 98.75 : 1.25 : 0.13 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound as a glass.

MS : 497 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 4.23 (2H, t), 3.98 (2H, t), 3.59 (1H, m), 2.64 (1H, dd), 2.57 (1H, dd), 1.58-1.83 (7H, m), 1.41 (9H, s), 1.08-1.37 (8H, m), 0.84 (2H, m).

Example 44:

N-(3-Azetidinyl)-5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide



A solution of tert-butyl 3-{[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]amino}-1-azetidinecarboxylate (Example 43) (160mg, 0.33mmol) in dichloromethane (10ml) was cooled to 0°C and treated with trifluoroacetic acid (7ml) and the resulting mixture was stirred at 0°C under a nitrogen atmosphere for 45 minutes. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane (x2).

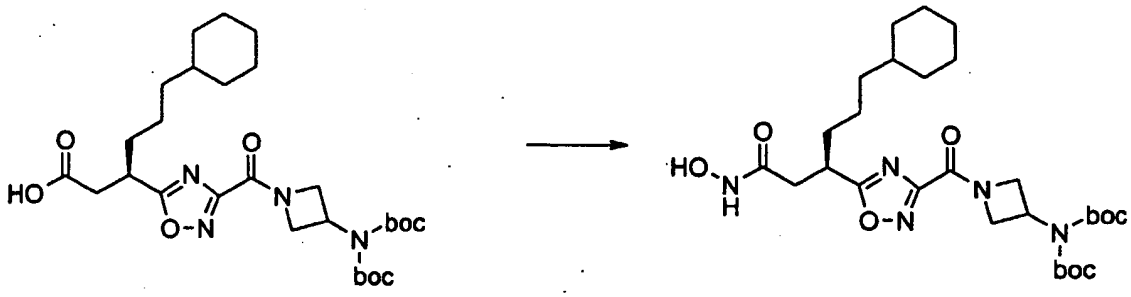
The residue was triturated with diethylether, filtered and dried to afford the title compound as a white solid (123mg).

MS : 380 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.83 (1H, m), 4.30 (4H, d), 3.58 (1H, m), 2.50-2.70 (2H, m), 1.77 (2H, m), 1.62 (5H, m), 1.08-1.39 (8H, m), 0.83 (2H, m).

Example 45:

Di(tert-butyl) 1-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinylimidodicarbonate



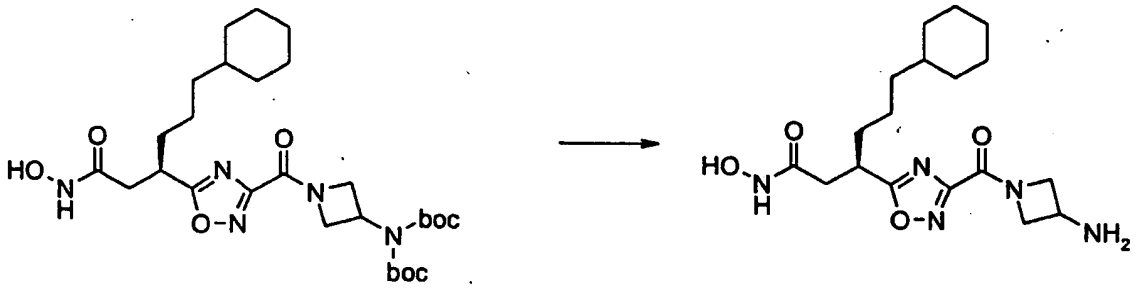
A solution of (3R)-3-[3-({3-[bis(tert-butoxycarbonyl)amino]-1-azetidinyl}carbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid (Preparation 80) (430mg, 0.76mmol) and N-methylmorpholine (167µl, 1.52mmol) in anhydrous tetrahydrofuran (20ml) was cooled to 0°C, treated with isobutyl chloroformate (120µl, 0.93mmol) and stirred under a nitrogen atmosphere for 2 hours. O-(Trimethylsilyl)hydroxylamine (280µl, 2.29mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (2x25ml) and brine (25ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of 98.75 : 1.25 : 0.13 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound as a sticky foam.

MS : 578 ($M-H^-$)

^{1}H-NMR (CD_3OD) δ : 4.88 (1H, m), 4.62 (1H,m), 4.40 (1H, t), 4.24 (1H,m), 3.60 (1H, m), 2.65 (1H, dd), 2.56 (1H, dd), 1.58-1.80 (6H, m), 1.50 (18H, s), 1.08-1.35 (9H, m), 0.83 (2H, m).

Example 46:

(3R)-3-{3-[(3-Amino-1-azetidinyl)carbonyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexyl-N-hydroxyhexanamide



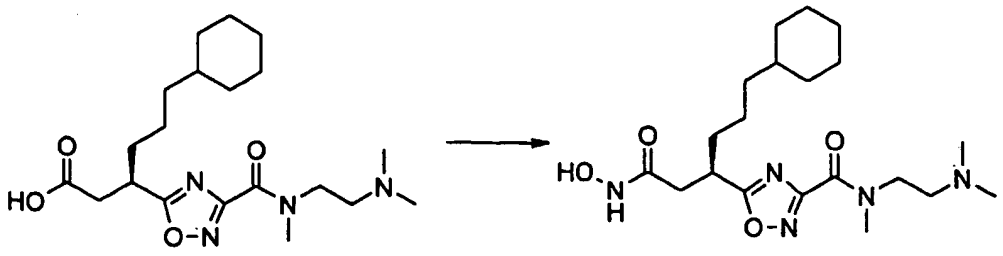
A solution of di(tert-butyl) 1-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinylimidodicarbonate (Example 45) (250mg, 0.43mmol) in dichloromethane (10ml) was cooled to 0°C and treated with trifluoroacetic acid (7ml) and the resulting mixture was stirred at 0°C under a nitrogen atmosphere for 45 minutes. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane (x2). The residue was triturated with diethylether, filtered and dried to afford the title compound as a white solid.

MS : 380 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.90 (1H, m), 4.53 (2H, m), 4.19 (2H, m), 3.58 (1H, m), 2.58-2.65 (2H, m), 1.76 (2H, m), 1.66 (5H, m), 1.06-1.38 (8H, m), 0.84 (2H,m).

Example 47:

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-[2-(dimethylamino)ethyl]-N-methyl-1,2,4-oxadiazole-3-carboxamide



A solution (3R)-6-cyclohexyl-3-(3-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 82) (450mg, 0.72mmol) and N-methylmorpholine (284µl, 2.53mmol) in dichloromethane (10ml) was cooled to 0°C, treated with isobutyl chloroformate (112µl, 0.87mmol) and stirred under an argon atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (355µl, 2.90mmol) was added and the mixture was stirred for 3.5 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (2.5ml) and stirred at room temperature for 20 minutes. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (20ml), dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of 97 : 3 : 0.3 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound as a gum (123mg).

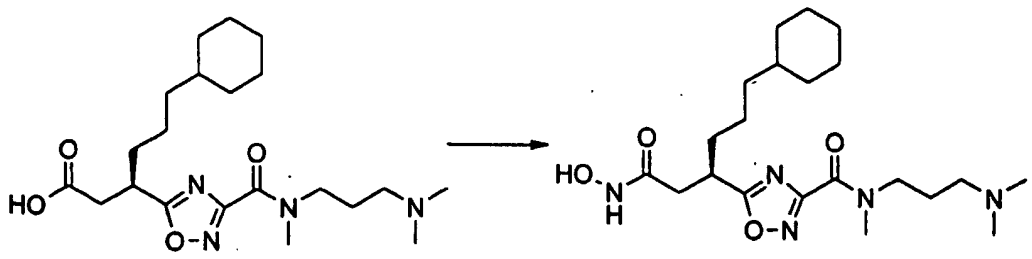
MS : 410 (MH^+)

Analysis : Found, C, 57.02; H, 8.50; N, 16.43%; $C_{20}H_{35}N_5O_4$. $0.25H_2O$. $0.1CH_2Cl_2$ requires C, 58.35; H, 8.72; N, 16.14%

^{1}H-NMR ($CDCl_3$) δ : 3.36-3.76 (3H, br d), 3.11 (3H, s), 2.45-2.74 (3H, m), 2.30 (1H, s), 2.25-2.35 (7H, m), 1.60-1.85 (7H, m), 1.05-1.40 (8H, m), 0.83 (2H, m).

Example 48:

5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-[3-(dimethylamino)propyl]-N-methyl-1,2,4-oxadiazole-3-carboxamide



A solution (3R)-6-cyclohexyl-3-(3-{[[3-(dimethylamino)propyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 84) (566mg, 0.88mmol) and N-methylmorpholine (390µl, 3.52mmol) in dichloromethane (10ml) was cooled to 0°C, treated with isobutyl chloroformate (340µl, 2.64mmol) and stirred under an argon atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (540µl, 4.40mmol) was added and the mixture was stirred for 4.5 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (2.5ml) and stirred at room temperature for 20 minutes. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (20ml), dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of 97 : 3 : 0.3 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound (150mg).

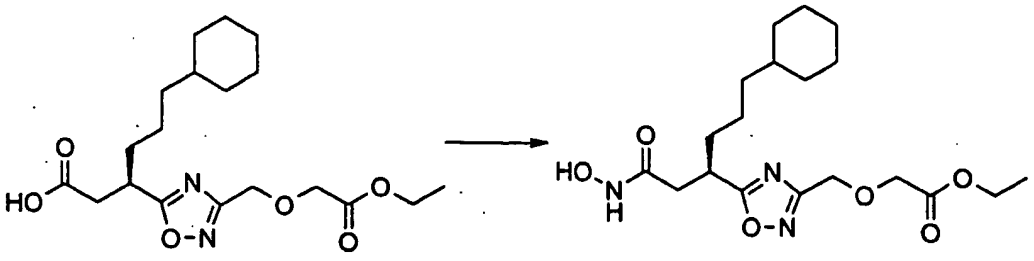
MS : 424 (MH^+)

Analysis : Found, C, 58.30; H, 8.64; N, 15.33%; $C_{21}H_{37}N_5O_4$. 0.2 H_2O. 0.08 CH_2Cl_2 requires C, 57.14; H, 8.50; N, 16.57%

^{1}H-NMR ($CDCl_3$) δ : 3.68 (2H, m), 3.30 (2H, m), 3.18 (3H, s), 2.28-2.40 (3H, m), 2.23 (6H, s), 1.58-1.88 (9H, m), 1.08-1.40 (8H, m), 0.88 (2H, m).

Example 49:

Ethyl [(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]acetate



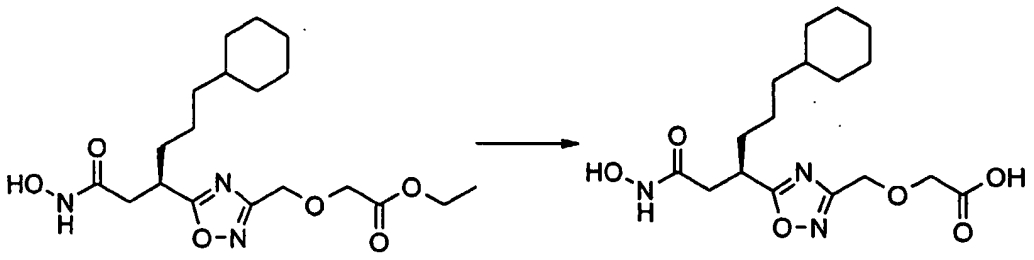
A solution of (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 87) (330mg, 0.86mmol) and N-methylmorpholine (160µl, 1.46mmol) in anhydrous tetrahydrofuran (14ml) was cooled to 0°C, treated with isobutyl chloroformate (120µl, 0.93mmol) and stirred under a nitrogen atmosphere for 2.5 hours. O-(Trimethylsilyl)hydroxylamine (350µl, 2.86mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 98 : 2 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol) to afford the title compound as a colourless oil (272mg).

MS : 420 (MNa^+)

^{1}H-NMR (CD_3OD) δ : 4.70 (2H, s), 4.20 (4H, m), 3.54 (1H, m), 2.61 (1H, dd), 2.50 (1H, dd), 1.60-1.80 (7H, m), 1.10-1.30 (11H, m), 0.82 (2H, m).

Example 50:

[(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]acetic acid



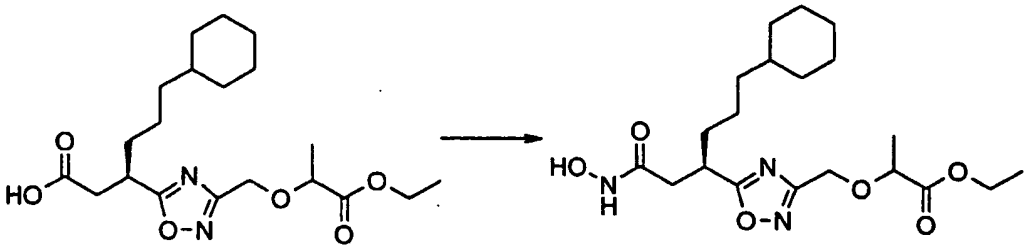
A solution of ethyl [(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]acetate (Example 49) (158mg, 0.40mmol) in 1,4-dioxan (4ml) and water (2ml) was treated with lithium hydroxide monohydrate (2mg, 0.48mmol) and stirred at room temperature for 2 hours. The reaction mixture was diluted with water and washed with diethylether (x2). The aqueous layer was acidified to pH 1 with hydrochloric acid (2M) and washed with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a colourless oil (141mg).

MS : 370 (MH+)

^{1}H-NMR (CD_3OD) δ : 4.70 (2H, s), 4.20 (2H, s), 3.55 (1H, m), 2.60 (1H, dd), 2.50 (1H, dd), 1.60-1.80 (7H, m), 1.10-1.30 (8H, m), 0.84 (2H, m).

Example 51:

Ethyl 2-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]propanoate



A solution of (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-1-methyl-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 89) (370mg, 0.93mmol) and N-methylmorpholine (170µl, 1.54mmol) in anhydrous tetrahydrofuran (15ml) was cooled to 0°C, treated with isobutyl chloroformate (130µl, 1.00mmol) and stirred under a nitrogen atmosphere for 2.5 hours. O-(Trimethylsilyl)hydroxylamine (380µl, 3.10mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (4ml) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient

system of 100 : 0 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol) to afford the title compound as a colourless oil (330mg).

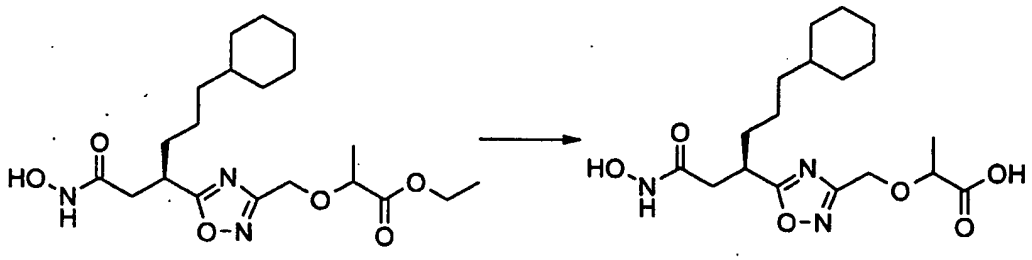
MS : 434 (MNa^+)

Analysis : Found, C, 57.55; H, 8.14; N, 9.81%; $C_{20}H_{33}N_3O_6$. 0.1 H_2O. 0.05 DCM requires C, 57.68; H, 8.04; N, 10.06%

^{1}H-NMR (CD_3OD) δ : 4.75 (1H, d), 4.59 (1H, d), 4.20 (3H, m), 3.55 (1H, m), 6.61 (1H, dd), (2.50 (1H, dd), 1.69-1.80 (7H, m), 1.38 (3H, d), 1.10-1.30 (11H, m), 0.82 (2H, m).

Example 52:

2-[(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]propanoic acid



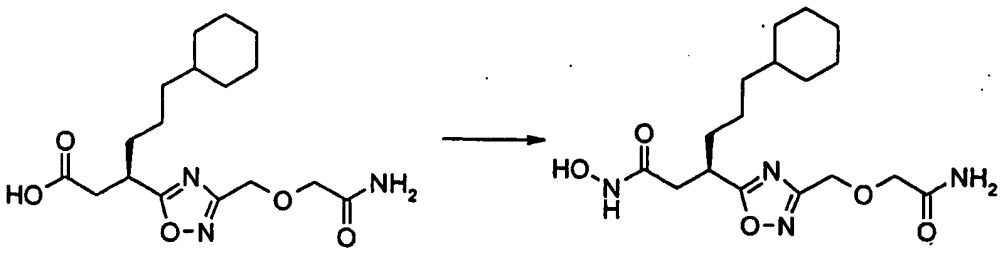
A solution of ethyl 2-[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)methoxy]propanoate (Example 51) (184mg, 0.45mmol) in 1,4-dioxan (4ml) and water (2ml) was cooled to 0°C and treated with lithium hydroxide monohydrate (2mg, 0.48mmol) and stirred at 0°C for 2 hours. The solvent was partially removed under reduced pressure and diluted with water and washed with diethylether (x2). The aqueous layer was acidified to pH 1 with hydrochloric acid (2M) and washed with ethyl acetate (x2). The combined organic layers were washed with brine, dries over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a colourless oil (160mg).

MS : 384 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.77 (1H, d), 4.59 (1H, d), 4.17 (3H, q), 3.45 (1H, m), 2.61 (1H, dd), 2.50 (1H, dd), 1.60-1.80 (7H, m), 1.39 (3H, d), 1.07-1.30 (8H, m), 0.83 (2H, m).

Example 53:

(3R)-3-{3-[(2-Amino-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexyl-N-hydroxyhexanamide



A solution of (3R)-3-{3-[(2-amino-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid (Preparation 91) (178mg, 0.50mmol) and N-methylmorpholine (100µl, 0.91mmol) in anhydrous tetrahydrofuran (8ml) was cooled to 0°C, treated with isobutyl chloroformate (70µl, 0.54mmol) and stirred under a nitrogen atmosphere for 2.5 hours. O-(Trimethylsilyl)hydroxylamine (200µl, 1.63mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 98 : 2 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol) and then neat methanol to afford the title compound as a colourless oil (60mg).

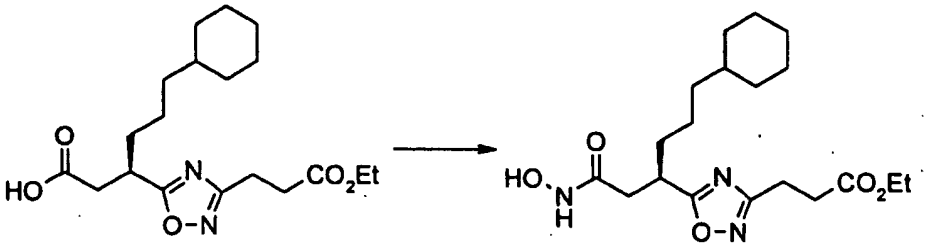
MS : 391 (MH^+)

Analysis : Found, C, 53.67; H, 7.55; N, 14.19%; $C_{17}H_{28}N_4O_5$. 0.2 CH_2Cl_2 requires C, 53.60; H, 7.43; N, 14.54%

^{1}H-NMR (CD_3OD) δ : 4.70 (2H, s), 4.08 (2H, s), 3.55 (1H, m), 2.45-2.70 (2H, m), 1.60-1.80 (7H, m), 1.10-1.30 (8H, m), 0.82 (2H, m).

Example 54:

Ethyl 3-(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)propanoate



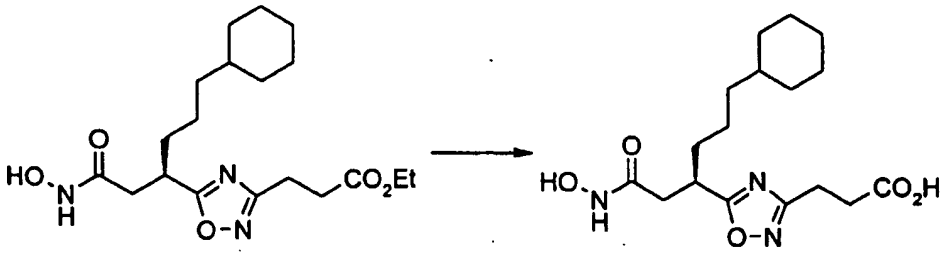
A solution of 3R)-6-cyclohexyl-3-[3-(3-ethoxy-3-oxopropyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 94) (110mg, 0.30mmol) and N-methylmorpholine (60µl, 0.54mmol) in anhydrous tetrahydrofuran (6ml) was cooled to 0°C, treated with isobutyl chloroformate (42µl, 0.32mmol) and stirred under a nitrogen atmosphere for 2.5 hours. O-(Trimethylsilyl)hydroxylamine (120µl, 1.00mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol and stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol) to afford the title compound as a yellow oil (94mg).

MS : 404 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.15 (2H, q), 3.52 (1H, m), 3.03 (2H, t), 2.78 (4H, m), 2.58 (1H, dd), 1.60-1.80 (7H, m), 1.10-1.35 (11H, m), 0.82 (2H, m).

Example 55:

3-(5-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)propanoic acid



A solution of ethyl 3-(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3- yl)propanoate (Example 54) (58mg, 0.15mmol) in 1,4-dioxan (2ml) and water (1ml) was treated with lithium hydroxide monohydrate (13mg, 0.31mmol) and stirred at room temperature for 2 hours. The reaction mixture was diluted with water and washed with diethylether (x2). The aqueous layer was acidified with hydrochloric acid (2M) (2ml) and washed with ethyl acetate (x2). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 : 0 (dichloromethane : methanol : acetic acid) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : acetic acid) to afford the title compound as an orange gum (36mg).

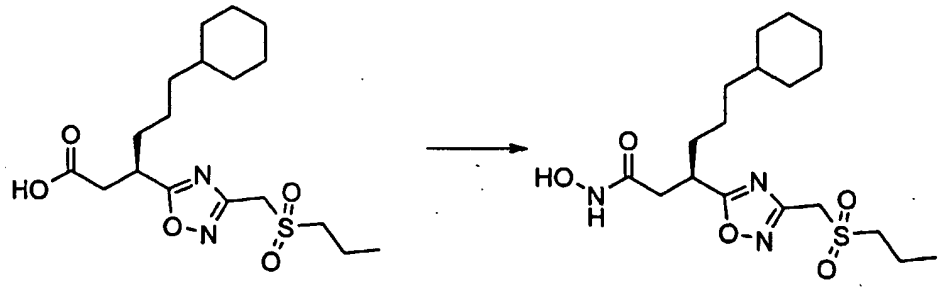
MS : 376 (MNa^+)

Analysis : Found, C, 55.98; H, 7.61; N, 11.12%; $C_{17}H_{27}N_3O_5$. 0.2 CH_2Cl_2 requires C, 55.77; H, 7.46; N, 11.34%

^{1}H-NMR (CD_3OD) δ : 3.50 (1H, m), 2.98 (2H, t), 2.76 (2H, t), 2.59 (1H, dd), 2.48 (1H, dd), 1.60-1.80 (7H, m), 1.07-1.35 (8H, m), 0.81 (2H, m).

Example 56:

(3R)-6-Cyclohexyl-N-hydroxy-3-{3-[(propylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanamide



A solution of (3R)-6-cyclohexyl-3-{3-[(propylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid (Preparation 97) (298mg, 0.77mmol) and 2,6-lutidine (135µl, 1.16mmol) in dichloromethane (10ml) was cooled to 0°C, treated with isobutyl chloroformate (100µl, 0.77mmol) and stirred under a nitrogen atmosphere for 1 hour. O-(Trimethylsilyl)hydroxylamine (310µl, 2.31mmol) was added and the mixture was stirred for 4 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (5ml) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with hydrochloric acid (1M) and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 (dichloromethane : methanol) gradually changing to 95 : 5 (dichloromethane : methanol) to afford the title compound as a white solid (140mg).

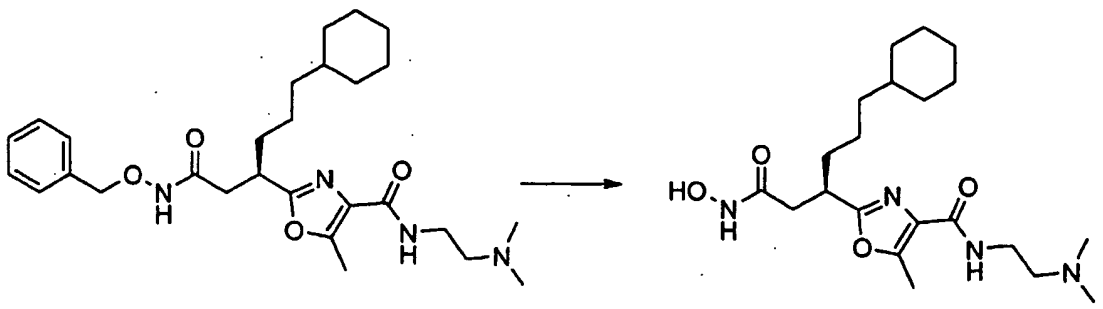
MS : 424 (MNa^+)

Analysis : Found, C, 53.65; H, 7.80; N, 10.26%; $C_{18}H_{31}N_3O_5S$ requires C, 53.84; H, 7.78; N, 10.47%

^{1}H-NMR (DMSO) δ : 10.39 (1H, br s), 8.65 (1H. br s), 4.70 (2H, s), 3.45 (1H, m), 3.20 (2H, obs), 2.50 (2H, obs), 1.76 (1H, m), 1.50-1.70 (7H, m), 1.08-1.25 (8H, m), 0.98 (3H, t), 0.80 (2H, m).

Example 57:

2-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-[2-(dimethylamino)ethyl]-5-methyl-1,3-oxazole-4-carboxamide



A solution 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N-[2-(dimethylamino)ethyl]-5-methyl-1,3-oxazole-4-carboxamide (Preparation 98) (193mg, 0.39mmol) in ethanol (10ml) was treated with ammonium formate (244mg, 3.90mmol) and 5% palladium on barium sulphate (100mg) and heated at 43°C, under a nitrogen atmosphere for 2 hours. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of 98 : 2 : 0.2 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound as a white solid (80mg).

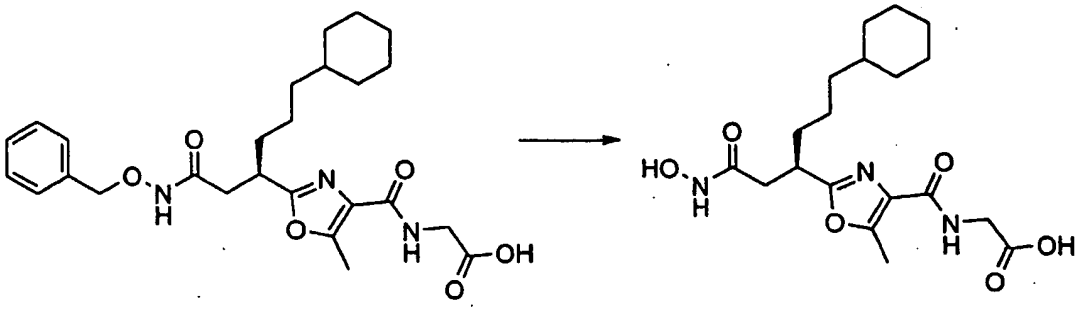
MS : 409 (MH^+)

Analysis : Found, C, 60.93; H, 9.06; N, 13.54%; $C_{21}H_{36}N_4O_4$. 0.2 H_2O requires C, 61.20; H, 8.90; N, 13.59%

^{1}H-NMR (d_6-DMSO) δ : 8.61 (1H, br s), 7.59 (1H, br s), 3.28 (2H, q), 3.18 (1H, obs), 2.45 (2H, obs), 2.35 (2H, t), 2.17 (6H, s), 1.50-1.65 (7H, m), 1.10-1.20 (7H, m), 0.80 (2H, m).

Example 58:

{[(2-{(1R)-4-Cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-5-methyl-1,3-oxazol-4-yl)carbonyl]amino}acetic acid



A solution ({[2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazol-4-yl]carbonyl}amino)acetic acid (Preparation 100) (60mg, 0.12mmol) in ethanol (3ml) was treated with ammonium formate (78mg, 1.23mmol) and palladium hydroxide (20mg) and heated at 43°C, under a nitrogen atmosphere for 4 hours. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of 99 : 1 : 0.1 (dichloromethane : methanol : acetic

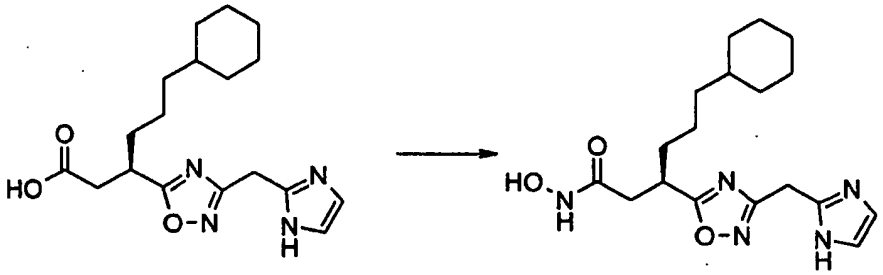
acid) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : acetic acid) to afford the title compound as a white solid (17mg).

MS : 394 $(M-H)^-$

^{1}H-NMR ($CDCl_3$) δ : 7.68 (1H, br s), 4.95-4.10 (2H, m), 3.34 (1H, m), 2.40-2.60 (5H, m), 1.50-1.80 (7H, m), 1.05-1.35 (8H, m), 0.81 (2H, m).

Example 59:

(3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(1*H*-imidazol-2-ylmethyl)-1,2,4-oxadiazol-5-yl]hexanamide



A solution of (3*R*)-6-cyclohexyl-3-[3-(1*H*-imidazol-2-ylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 103) (200mg, 0.43mmol) in anhydrous tetrahydrofuran (5ml) was treated with 1,1'-carbonyldiimidazole (77mg, 0.48mmol) and stirred under a nitrogen atmosphere for 30 minutes. *O*-(Trimethylsilyl)hydroxylamine (160µl, 1.30mmol) was added and the mixture was stirred for 18 hours. The mixture was then treated with methanol (4ml) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford a colourless oil which began to crystallise once a little methanol and dichloromethane were added. The solid was triturated with dichloromethane and dried under reduced pressure to afford the title compound as a solid (49mg).

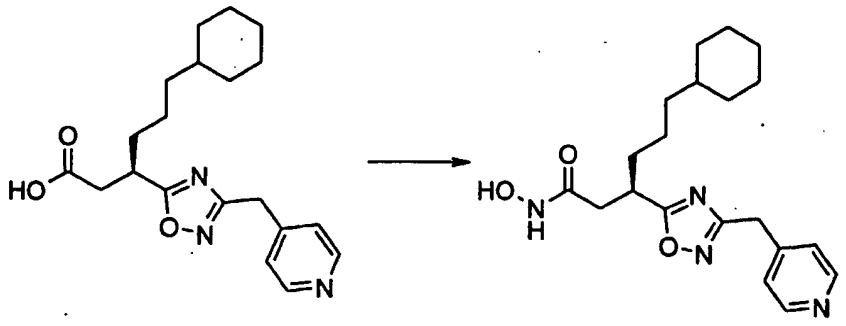
MS : 362 (MH^+)

Analysis : Found, C, 59.24; H, 7.42; N, 19.13%; $C_{18}H_{27}N_5O_3$. $0.2H_2O$ requires C, 59.22; H, 7.57; N, 19.18%

^{1}H-NMR (d_6-DMSO) δ : 10.38 (1H, s), 8.65 (1H, s), 7.70 (1H, s), 7.17 (1H, s), 6.88 (1H, s), 5.39 (2H, s), 3.42 (1H, m), 2.45 (2H, m), 1.5-1.70 (7H, m), 1.00-1.15 (8H, m), 0.78 (2H, m).

Example 60:

(3*R*)-6-cyclohexyl-*N*-hydroxy-3-[3-(4-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanamide



A solution of (3*R*)-6-cyclohexyl-3-[3-(4-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 106) (380mg, 0.96mmol) in dichloromethane (10ml) was treated with 1,1'-carbonyldiimidazole (156mg, 0.96mmol) and stirred under a nitrogen atmosphere for 1 hour. *O*-(Trimethylsilyl)hydroxylamine (388µl, 2.89mmol) was added and the mixture was stirred for 3.5 hours. The mixture was then treated with methanol (5ml) and stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 95 : 5 (dichloromethane : methanol) to afford a white solid. Analysis suggests that 10% imidazole remains. The solid was dissolved in ethyl acetate and washed with water, dried over anhydrous magnesium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a white solid (128mg).

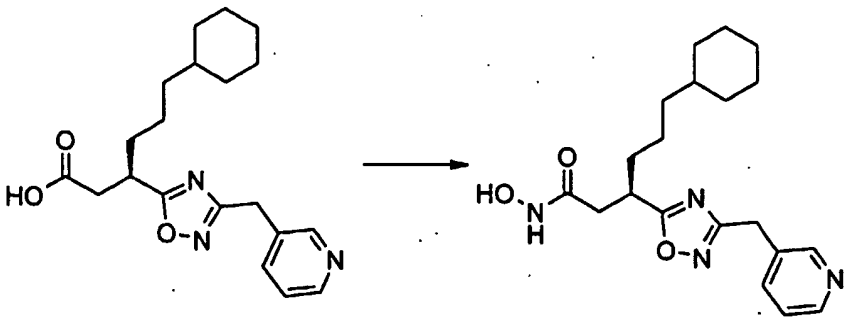
MS : 373 (MH^+)

Analysis : Found, C, 64.13; H, 7.59; N, 14.86%; $C_{20}H_{28}N_4O_3$ requires C, 64.49; H, 7.58; N, 15.04%

^{1}H-NMR (d_6-DMSO) δ : 10.38 (1H, s), 8.65 (1H, s), 8.49 (2H, d), 7.25 (2H, d), 4.10 (2H, s), 3.39 (1H, m), 2.20 (2H, m), 1.50-1.65 (7H, m), 1.00-1.20 (8H, m), 0.87 (2H, m).

Example 61:

(3*R*)-6-Cyclohexyl-*N*-hydroxy-3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanamide



A solution of (3*R*)-6-cyclohexyl-3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 109) (410mg, 1.04mmol) in dichloromethane (10ml) was treated with 1,1'-carbonyldiimidazole (169mg, 1.04mmol) and stirred under a nitrogen atmosphere for 1 hour. *O*-(Trimethylsilyl)hydroxylamine (418µl, 3.12mmol) was added and the reation mixture was stirred for 18 hours. The reaction mixture was then treated with methanol (5ml) and stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water (3x30ml) and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a solvent gradient of 100 : 0 (dichloromethane : methanol) gradually changing to 95 : 5 (dichloromethane : methanol) to afford a white waxy solid. The solid was recrystallised from ethyl acetate to afford the title compound as a white solid (128mg).

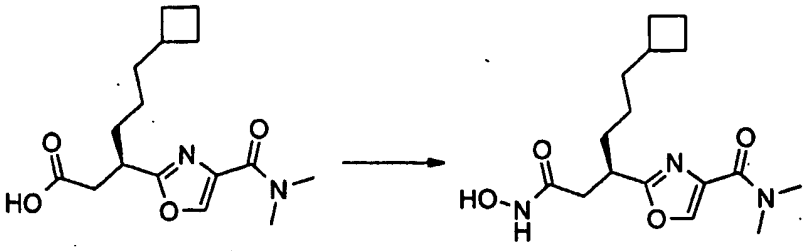
MS : 373 (MH^+)

Analysis : Found, C, 64.53; H, 7.63; N, 14.53%; $C_{20}H_{28}N_4O_3$.0.15 EtOAc requires C, 64.15; H, 7.63; N, 14.53%

^{1}H-NMR (d_6-DMSO) δ : 10.36 (1H, s), 8.62 (1H, s), 8.54 (1H, s), 8.43 (1H, d), 7.65 (1H, d), 7.30 (1H, m), 4.10 (2H, s), 3.40 (1H, m), 2.70 (1H, m), 2.40 (1H, m), 1.50-1.70 (7H, m), 1.00-1.20 (8H, m), 0.76 (2H, m).

Example 62:

2-{(1*R*)-4-Cyclobutyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-*N*,*N*-dimethyl-1,3-oxazole-4-carboxamide



A solution of (3*R*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}hexanoic acid (Preparation 121) (155mg, 0.50mmol) and *N*-methylmorpholine (90µl, 0.82mmol) in anhydrous tetrahydrofuran (8ml) was cooled to 0°C, treated with isobutyl chloroformate (90µl, 0.70mmol) and stirred under a nitrogen atmosphere for 2 hours. *O*-(Trimethylsilyl)hydroxylamine (200µl, 1.63mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The mixture was then treated with methanol (2ml) and stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 98 : 2 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol). The solid was triturated with diethyl ether, filtered and dried under reduced pressure to afford the title compound as a white solid (64mg).

MS : 346 (MNa^+)

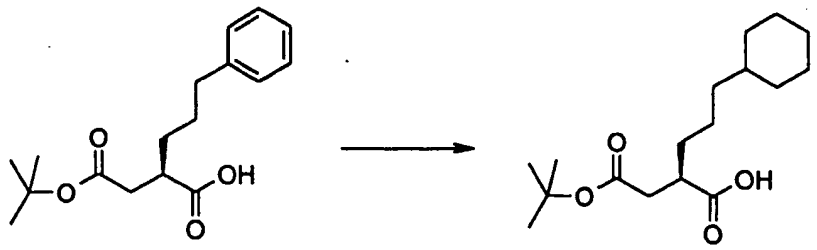
Analysis : Found, C, 59.03; H, 7.81; N, 12.92%; $C_{16}H_{25}N_3O_4$. 0.1 H_2O requires C, 59.10; H, 7.81; N, 12.92%

^{1}H-NMR (d_6-DMSO) δ : 10.45 (1H, s), 8.78 (1H, s), 8.38 (1H, s), 3.25 (1H, t), 3.28 (3H, s), 2.90 (3H, s), 2.40 (1H, dd), 2.28 (1H, dd), 2.12 (1H, m), 1.91 (2H, m), 1.70 (2H, m), 1.57 (2H, m), 1.45 (2H, m), 1.27 (2H, m), 1.02 (2H, m).

Preparation 1 : (2R)-2-[2-(tert-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid

Route A:

(2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid



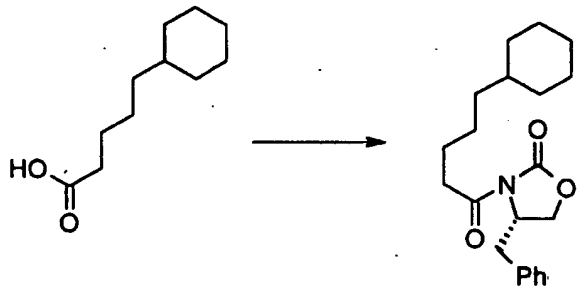
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenylpentanoic acid (Syn. Lett.; 1998; 637-639) (10.00g, 34.2mmol) in acetic acid (120ml) was treated with 5% Rhodium on alumina catalyst, pressurised to 60psi with hydrogen in a sealed vessel and stirred at room temperature for 17 hours. The mixture was filtered through a pad of Arbocel® and the solvent was removed from the filtrate under reduced pressure. The residue was azeotroped from toluene to afford the title compound (7.53g).

MS : 299 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 2.80 (1H, m), 2.61 (1H, m), 2.38 (1H, m), 1.75-1.56 (7H, m), 1.55-1.04 (17H, m), 0.84 (2H, m).

Route B:

(4S)-4-Benzyl-3-(5-cyclohexylpentanoyl)-1,3-oxazolidin-2-one



A solution of 5-cyclohexylpentanoic acid (63.50g, 345mmol) in N,N-dimethylformamide (0.5ml) and dichloromethane (350ml) was cooled to 5°C and treated dropwise with oxalyl chloride (31.6ml, 362mmol) over 30 minutes. The mixture was stirred at 0°C for 3 hours then the solvent was removed under reduced pressure to afford 5-cyclohexylpentanoyl chloride as a pale yellow solid (70.0g).

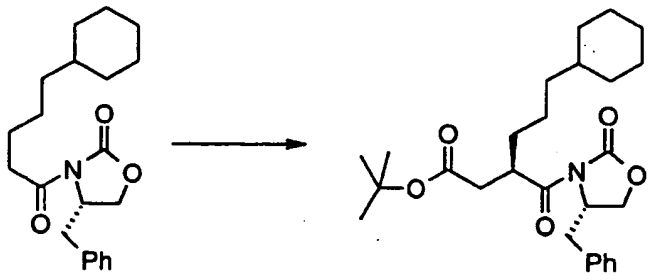
A solution of n-butyllithium (100ml, 250mmol, 2.5M in hexanes) was added via a cannula to a solution of (4S)-4-benzyl-1,3-oxazolidin-2-one (44.30g, 250mmol) in anhydrous tetrahydrofuran (400ml) at -78°C. The yellow solution was then stirred for 45 minutes. A solution of 5-

cyclohexylpentanoyl chloride (55.5g, 275mmol) in tetrahydrofuran (100ml) was then added over 1 hour. The mixture was stirred at -78°C for 30 minutes then warmed to room temperature over 1 hour. The mixture was quenched with an aqueous solution of ammonium chloride (20% w/v, 400ml) and extracted with ethyl acetate. The layers were separated and the organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The solid was recrystallised from hexane (500ml) to afford the title compound as a white solid (81.0g).

MS: 344 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 7.41-7.13 (5H, m), 4.68 (1H, m), 4.27-4.02 (2H, m), 3.31 (1H, dd, J=16, 4Hz), 3.06-2.70 (3H, m), 1.81-1.53 (7H, m), 1.49-1.04 (8H, m), 0.88 (2H, m)

tert-Butyl 3-{[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-6-cyclohexylhexanoate

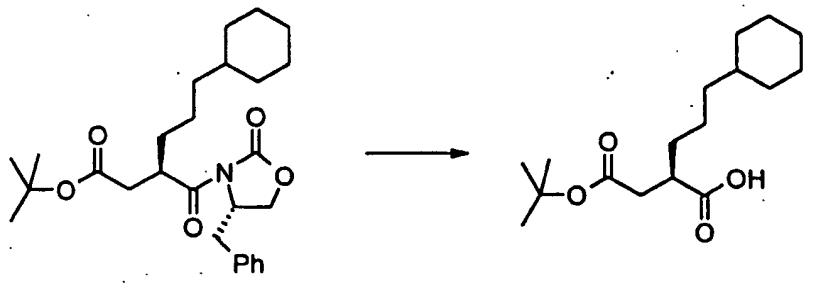


A solution of (4S)-4-benzyl-3-(5-cyclohexylpentanoyl)-1,3-oxazolidin-2-one (70.0g, 204mmol) in anhydrous tetrahydrofuran (650ml) was cooled to -70°C and treated dropwise with sodium hexamethyldisilazide (1M in tetrahydrofuran, 224ml, 224mmol) over 45 minutes. The mixture was stirred for a further 45 minutes before being treated with t-butylbromoacetate (31.6ml, 214mmol). This mixture was stirred at -70°C for 30 minutes then warmed to -30°C and quenched with an aqueous solution of ammonium chloride (20%w/v, 400ml) and warmed to room temperature. The mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The solid was recrystallised from hexane to afford the title compound as a white solid (71.4g).

MS: 458(MH^+)

^{1}H-NMR ($CDCl_3$) δ : 7.41-7.13 (5H, m), 4.66 (1H, m), 4.23-4.03 (3H, m), 3.35 (1H, dd, J=16, 4Hz), 2.95-2.68 (3H, m), 2.47 (1H, m), 1.80-1.07 (24H, m), 0.85 (2H, m)

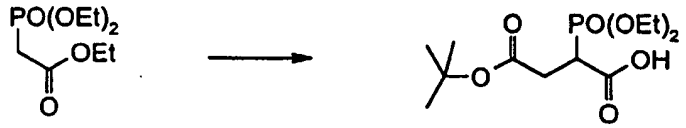
2-[2-(tert-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid



A solution of tert-butyl 3-{[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-6-cyclohexylhexanoate (64.0g, 139.9mmol) in tetrahydrofuran : water (3:1, 800ml) was cooled to 5°C then treated sequentially with hydrogen peroxide (30%w/v water, 87ml, 769mmol) then lithium hydroxide hydrate (10.0g, 238mmol). The reaction was stirred for 1 hour then quenched by dropwise addition of an aqueous solution of sodium thiosulphate (500ml) keeping the temperature below 20°C. The mixture was extracted with ethyl acetate (discarded) and the aqueous phase was acidifed to pH 2 with solid citric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (2 : 1) gradually changing to hexane : ethyl acetate (1 : 1) to afford the title compound (40.7g)

Route C:

3-(Diethoxyphosphoryl)succinic acid 1-tert-butyl ester



Triethylphosphonoacetate (102g, 0.45 mol) was added dropwise over 11 min to a stirred solution of potassium tert-butoxide (60g, 0.54 mol) in THF (500ml), at 0°C, under nitrogen. The mixture was stirred for 1 hour at 0°C and then dichloromethane (300ml) was added and the reaction mixture was warmed to 25-30°C. The mixture was stirred at 25-30°C for 1 hour and then added dropwise over 33 minutes to a solution of tert-butyl bromoacetate (96g, 0.49 mol) in THF

(500ml), at 0°C, under nitrogen. The mixture was stirred at 0-5°C for 2 hours and then a solution of citric acid (174g, 0.91 mol) in demineralised water (250ml) was added. The mixture was concentrated in vacuo to remove most of the THF and then toluene (750ml) was added. The organic phase was separated, washed with brine (2x150ml) and concentrated in vacuo to leave a colourless oil. The oil was taken up in ethanol and a solution of potassium hydroxide (36.g, 0.64mol) in demineralised water (150ml) was added dropwise over 15 mins. The mixture was stirred at 0°C for 4 hours and then a solution of citric acid (158 g, 0.82 mol) in demineralised water (600ml), and toluene (600ml), were added. The organic phase was separated and the aqueous phase was re-extracted with toluene (600ml). The combined organic phases were washed with demineralised water (2x150ml) and concentrated in vacuo to leave a white solid. Toluene (150ml) was added and the slurry was re-concentrated in vacuo to leave a white solid. The product was purified by crystallisation from tert-butylmethyl ether (300ml) and cyclohexane (600ml) to give the title compound as a solid (79g).

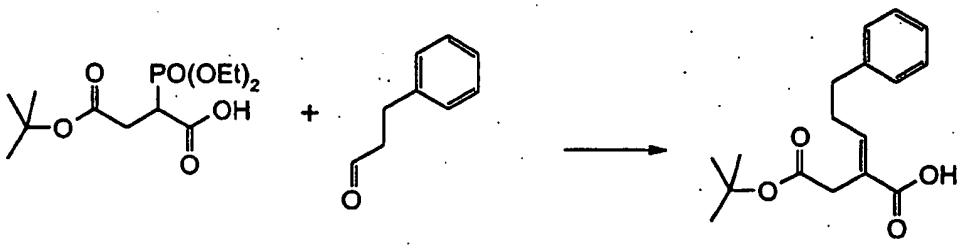
^{1}H-NMR ($CDCl_3$) δ : 4.20-4.10 (4H, m), 3.49-3.36 (1H, m), 3.00-2.85 (1H, m), 2.72-2.60 (1H, m), 1.20 (9H, s), 1.37-1.27 (6H, m)

Alternative preparation:

Triethylphosphonoacetate (12.0Kg, 53.5 mol) was added over 30 minutes to a stirred solution of potassium *tert*-butoxide (7.20Kg, 64.2 mol) in THF (118 litres), between 0 and 5°C, under nitrogen. The mixture was warmed to 25-30°C where it was stirred for 1 hour and then added over 45 minutes to a solution of *tert*-butyl bromoacetate (11.5Kg, 59.0 mol) in THF (28 litres), between 0 and 5°C, under nitrogen. The mixture was stirred at 0-5°C for 1 hour and then demineralised water (6.1 litres) and ethanol (30 litres) were added. A solution of potassium hydroxide (4.2Kg, 75.0 mol) in demineralised water (84 litres) was then added over 2 hours, between -5 and 0°C. The mixture was stirred at -10°C for 16 hours and then a solution of citric acid (16.5Kg, 85.8 mol) in demineralised water (32 litres) was added. The mixture was concentrated *in vacuo* to a volume of 180 litres and then ethyl acetate (90 litres) was added. The organic phase was separated and the aqueous phase was re-extracted with ethyl acetate (30 litres). The combined organic phases were washed with water (30 litres) and then stripped and replaced with cyclohexane by distillation at atmospheric pressure, at a constant volume of 72 litres. *tert*-Butylmethyl ether (18 litres) was added and the mixture was stirred at ambient temperature for 12 hours and then filtered. The residue was washed with a mixture of cyclohexane (16 litres) and *tert*-butylmethyl ether (3.6 litres) then dried *in vacuo* for 16 hours to give the title compound as a colourless solid (10.0Kg, 60%).

^{1}H-NMR ($CDCl_3$) δ : 4.20-4.10 (4H, m), 3.49-3.36 (1H, m), 3.00-2.85 (1H, m), 2.72-2.60 (1H, m), 1.20 (9H, s), 1.37-1.27 (6H, m)

(E)-2-[2-(tert-Butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid

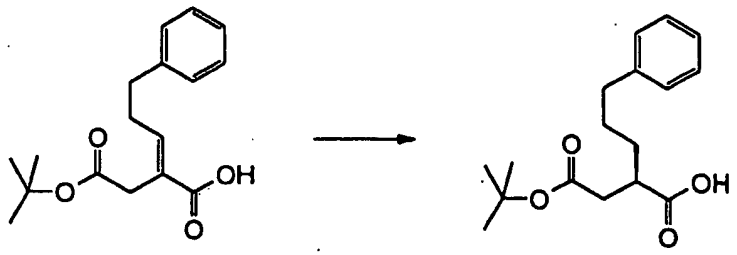


A solution of 3-(diethoxyphosphoryl)succinic acid 1-*tert*-butyl ester (100g, 0.32mol) in THF (300ml) was added dropwise over 15 min to a stirred solution of potassium *tert*-butoxide (110g, 0.98mol) in THF (300ml), between –10 and -5°C, under nitrogen. The mixture was stirred at -10°C for 15 min and then a solution of hydrocinnamaldehyde (46.8g, 0.35mmol) in THF (100ml) was added dropwise over 15 min, between –13 and –8°C. The mixture was stirred at –10°C for 30 min and then a solution of citric acid (111g, 0.58mol) in demineralised water (500ml), and ethyl acetate (500ml), were added. The pH was adjusted to pH 4 with aqueous sodium hydroxide solution (50%) and the phases were separated. The aqueous fraction was washed with ethyl acetate (500ml) and the combined organic fractions were washed with saturated sodium bicarbonate solution (500ml), citric acid solution (10%, 500ml) and demineralised water (500ml) and then concentrated *in vacuo*. The resulting solid was slurried in cyclohexane (470ml) for 1 hour and then the mixture was filtered. The residue was washed with cyclohexane (2x50ml) and dried *in vacuo* to leave the title compound as a colourless solid (76g, 81%).

MS : 289 $[(M-H)]^-$

^{1}H-NMR ($CDCl_3$) δ : 7.33-7.16 (5H, m), 7.05 (1H, br t), 3.20 (2H, s), 2.89 (2H, br t), 2.50 (2H, br dd), 1.41 (9H, s)

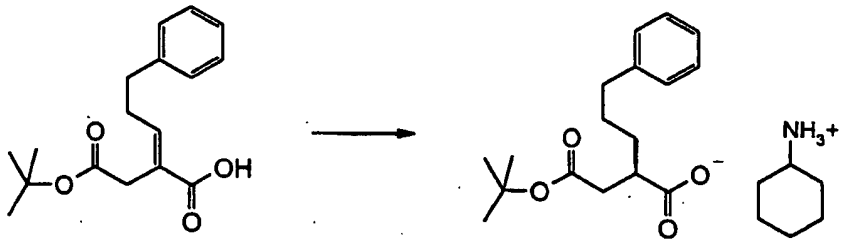
(R)-2-[2-(tert-Butoxy)-2-oxoethyl]-5-phenylpentanoic acid



A stirred solution of (E)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid (100g, 0.34mol), cyclohexylamine (39ml, 0.34mol) and [(S)-2,2'-bis(diphenylphosphino-1,1'-binaphthyl]chloro(p-cymene)ruthenium chloride (0.64g, 0.69mmol) in methanol (1000ml) was heated to 60°C, under hydrogen (60p.s.i.), for 42 hours and then allowed to cool to room temperature. The mixture was filtered through celite and then concentrated in vacuo to a yellow solid which was purified by re-crystallisation from acetone (850ml). The resulting solid was partitioned between ethyl acetate (1200ml) and citric acid solution (10%, 1200ml) and the organic phase was separated, washed with demineralised water (1200ml) and concentrated in vacuo to leave the title compound as an oil (80g).

^{1}H-NMR ($CDCl_3$) δ : 7.30-7.17 (5H, m), 2.85-2.78 (1H, m), 2.66-2.58 (3H, m), 2.37 (1H, br dd), 1.75-1.51 (4H, m), 1.40 (9H, s)

Preparation of cyclohexylamine salt:

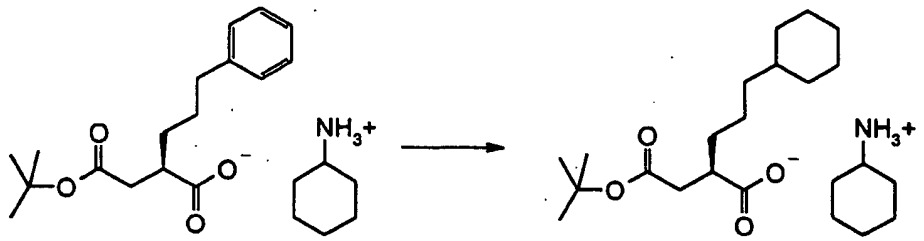


A stirred solution of cyclohexylamine (266ml, 2.32 mol), (*E*)-2-[2-(*tert*-butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid (688g, 2.37 mol) and [(*S*)-2,2'-bis(diphenylphosphino-1,1'-binaphthyl]chloro(*p*-cymene)ruthenium chloride (4.4g, 4.7 mmol) in methanol (6.9 litres) was heated to 60°C, under hydrogen (60p.s.i.), for 47 hours and then allowed to cool to room temperature (enantiomeric excess= 88%). The mixture was filtered through celite and then the solvent was stripped and replaced with acetone by distillation at atmospheric pressure, at a constant volume of 4.2 litres. The resulting suspension was cooled to room temperature where it was stirred for 4 hours and then filtered. The residue was washed with acetone (2x 1 litre) and

then dried *in vacuo* at 45°C for 16 hours to leave the title compound as a colourless solid (590g, 64%, enantiomeric excess=98.9%).

^{1}H-NMR (CD_3OD) δ : 7.23-7.09 (5H, m), 3.05-2.98 (1H, m), 2.64-2.56 (3H, m), 2.53 (1H, dd, *J* 15.2, 7.2Hz), 2.23 (1H, dd, *J* 15.2, 7.2Hz), 2.00-1.97, (2H, m), 1.85-1.81 (2H, m), 1.72-1.20 (10H, m), 1.40 (9H, s)

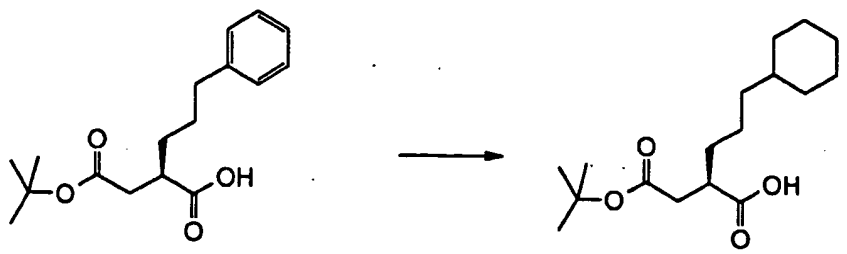
(*R*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid cyclohexylamine salt



(*R*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-phenylpentanoic acid cyclohexylamine salt (691g, 1.77 mol) and ethyl acetate (7.0 litres) were added to an aqueous solution of citric acid (10%, 6.3 litres) and the organic phase was separated, washed with water (7.0 litres) and concentrated *in vacuo* to a yellow oil. A solution of the oil and 5% rhodium on carbon (51.6g) in methanol (7.0 litres) was stirred at ambient temperature, under hydrogen (150p.s.i.) for 48 hours and then filtered through celite. To the filtrate was added cyclohexylamine (202ml, 1.77 mol) and the methanol solution was stripped and replaced with methylethyl ketone by distillation at atmospheric pressure, to a volume of 5.5 litres. The mixture was allowed to cool to ambient temperature where it was stirred for 48 hours and then filtered. The residue was washed with methylethyl ketone (2x 500ml) and then dried *in vacuo* at 45°C for 4 hours to leave the title compound as a colourless solid (495g, 71%).

^{1}H-NMR (CD_3OD) δ : 3.06-2.99 (1H, m), 2.63-2.56 (1H, m), 2.53 (1H, dd, *J* 15.2, 7.2Hz), 2.23 (1H, dd, *J* 15.2, 7.2Hz), 2.02-1.97 (2H, m), 1.77-1.15 (21H, m), 1.43 (9H, s), 0.93-0.82 (2H, m)

(R)-2-[2-(tert-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid

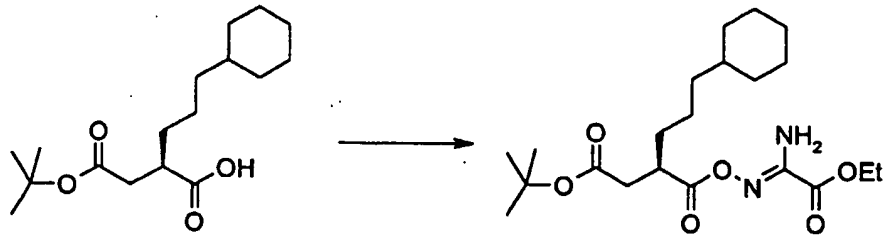


A solution of (R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenylpentanoic acid (2.2g, 7.5mmol) and 5%Rh/C (0.22g) in methanol (220ml) was stirred at room temperature, under hydrogen (150p.s.i.) for 24 hours and then filtered through celite. The filtrate was concentrated in vacuo to leave the title compound as an oil (2.0g).

^{1}H-NMR ($CDCl_3$) δ : 2.82-2.76 (1H, m), 2.60 (1H, br dd), 2.37 (1H, br dd), 1.70-1.60 (6H, m), 1.51-1.30 (3H, m), 1.42 (9H, s), 1.23-1.11 (6H, m), 0.96-0.80 (2H, m)

Preparation 2 :

tert-Butyl (3R)-3-[({[(Z)-1-amino-2-ethoxy-2-oxoethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate



A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (7.53g, 25.2mmol) in 1,4-dioxane (175ml) was treated with 1-hydroxybenzotriazole hydrate (3.75g, 27.8mmol) and the mixture cooled to 0°C. N,N'-Dicyclohexylcarbodiimide (5.47g, 26.5mmol) was then added and the mixture was stirred for 3 hours being allowed to warm to room temperature over this time. The mixture was then filtered and washed with 1,4-dioxane (2x50ml). The filtrate was then treated with sodium carbonate (4.01g, 37.8mmol) and ethyl 2-amino-2-(hydroxyimino)acetate (J.Org.Chem.;23; 1958; 1794) (3.33g, 25.2mmol). The resulting mixture was stirred at room temperature for 17 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate (x2). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under

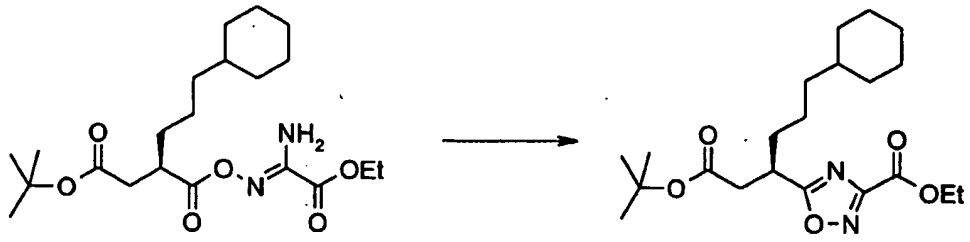
reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (30 : 70) gradually changing to ethyl acetate : pentane (50 : 50) to afford the title compound as a white solid (6.50g).

MS : 413 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 5.71 (2H, br s), 4.39 (2H, q), 2.92 (1H, m), 2.67 (1H, dd), 2.44 (1H, dd), 1.75-1.32 (22H, m), 1.26-1.04 (5H, m), 0.84 (2H, m).

Preparation 3 :

Ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate



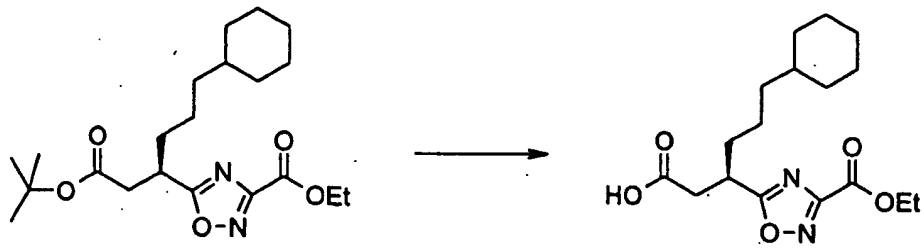
A solution of tert-Butyl (3R)-3-[({[(Z)-1-amino-2-ethoxy-2-oxoethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate (Preparation 2) (21.0g, 50.82mmol) in xylene (400ml) was heated at 130°C for 17 hours, then allowed to cool to room temperature. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (5 : 95) gradually changing to ethyl acetate : pentane (20 : 80) to afford the title compound as a colourless oil (20.0g).

MS : 395 (MH^+), 412 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 4.51 (2H, m), 3.54 (1H, m), 2.86 (1H, dd), 2.65 (1H, dd), 1.86-1.57 (7H, m), 1.50-1.33 (12H, m), 1.30-1.03 (8H, m), 0.82 (2H, m).

Preparation 4 :

(3R)-6-Cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



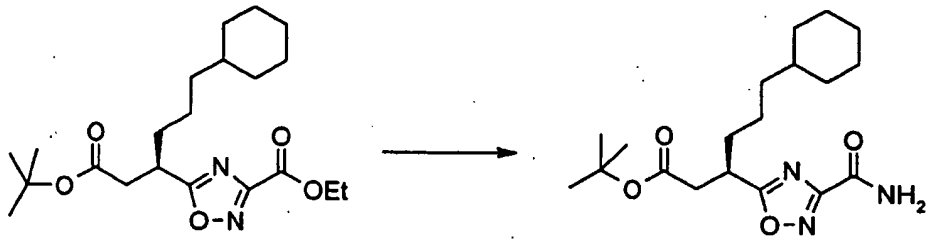
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (820mg, 2.08mmol) in dichloromethane (10ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The mixture was stirred for 2.5 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue azeotroped with toluene (x2). The residue was then dissolved in ethyl acetate, washed sequentially with an aqueous solution of sodium dihydrogen citrate and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil (740mg).

MS : 339 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.49 (2H, q J=7Hz), 3.57 (1H, m), 3.05 (1H, dd J=17, 8Hz), 2.81 (1H, dd J=17, 4Hz), 1.92-1.55 (7H, m), 1.45 (3H, t J=7Hz), 1.35-1.02 (8H, m), 0.84 (2H, m)

Preparation 5 :

tert-Butyl (3R)-3-[3-(aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-phenylhexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (400mg, 1.01mmol) in ethanol saturated with ammonia gas (20ml) was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (90 : 10) gradually changing to hexane : ethyl acetate (60 : 40) to afford the title compound as a white solid (260mg).

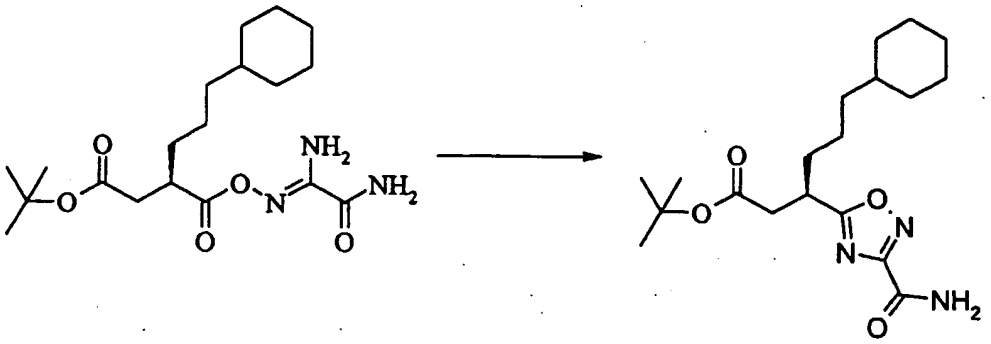
MPt : 77-79°C

MS : 366 (MH^+), 383 (MNa^+)

Analysis : Found C, 62.42; H, 8.59; N, 11.48%; $C_{19}H_{31}N_3O_4$ requires C, 62.44; H, 8.55; N, 11.50%

^{1}H-NMR ($CDCl_3$) δ : 6.80 (1H, br s), 5.90 (1H, br s), 3.53 (1H, m), 2.87 (1H, dd, J=17, 9Hz), 2.66 (1H, dd, J=17, 5Hz), 1.90-1.50 (7H, m), 1.46-1.02 (17H, m), 0.83 (2H, m).

Alternative preparation of tert-butyl (3R)-3-[3-(aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexyl-hexanoate:

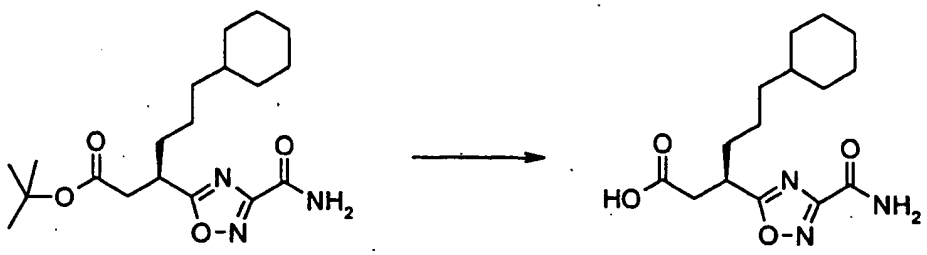


tert-Butyl(3R)-3-[({[(Z)-1,2-diamino-2-oxoethylidene]amino}oxy)carbonyl]-6-cyclohexyl-hexanoate (Preparation 101) (4.10g, 10.7 mmol) in mixed xylenes (25 ml) was heated to reflux for 48 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with isocratic system of n-hexane:ethyl acetate (75:25) to afford a yellow oil. The oil was crystallised from cyclohexane to afford the title compound as a colourless solid (0.60 g).

^{1}H-NMR ($CDCl_3$) δ : 6.80 (1H, br s), 5.90 (1H, br s), 3.53 (1H, m), 2.87 (1H, dd, *J*=17, 9 Hz), 2.66 (1H, dd, *J*=17, 5 Hz), 1.90-1.50 (7H, m), 1.46-1.02 (17H, m), 0.93-0.82 (2H, m).

Preparation 6:

(3R)-3-[3-(Aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



A solution of tert-butyl (3R)-3-[3-(aminocarbonyl)-1,2,4-oxadiazol-5-yl]-6-phenylhexanoate (Preparation 5) (250mg, 0.68mmol) in dichloromethane (10ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The mixture was stirred for 2 hours, being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue was azeotroped with toluene (x2) then hexane to afford the title compound as a white solid (204mg).

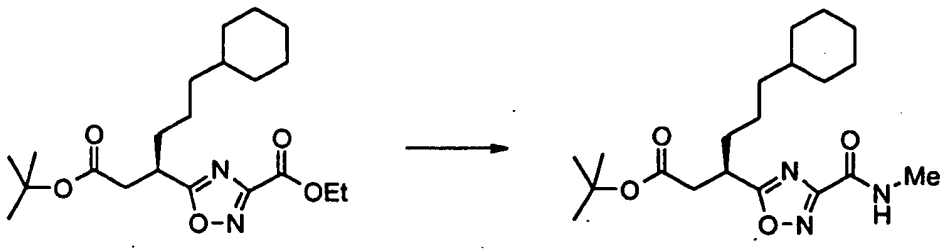
MPt. : 172-174°C

Analysis : Found C, 58.03; H, 7.48; N, 13.38%; $C_{15}H_{23}N_3O_4$ requires C, 58.24; H, 7.49; N, 13.19%

^{1}H-NMR (CD_3OD) δ : 3.55 (1H, m), 2.93 (1H, dd, J=17, 9Hz), 2.80 (1H, dd, J=17, 4Hz), 1.84-1.59 (7H, m), 1.40-1.08 (8H, m), 0.86 (2H, m).

Preparation 7 :

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(methylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (4.70g, 11.9mmol) in ethanol (80ml) was treated with methylamine (33% w/v in ethanol, 12.0ml, 96.0mmol) and the solution was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl

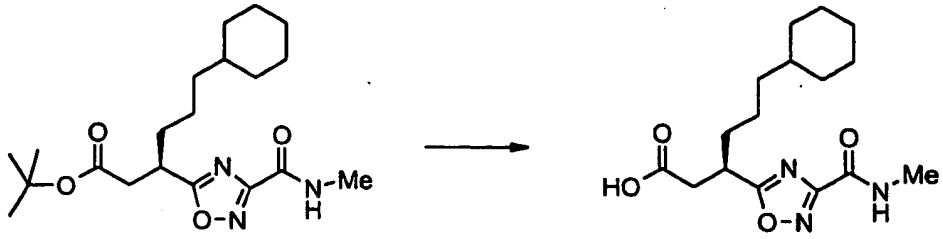
acetate (9 : 1) gradually changing to dichloromethane : ethyl acetate (8 : 2) to afford the title compound as a pale yellow oil which crystallised on standing (4.23g).

MS : 380 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 6.97 (1H, br m), 3.48 (1H, m), 3.04 (3H, d), 2.84 (1H, dd, J=17, 9Hz), 2.66 (1H, dd, J=17, 4Hz), 1.84-1.55 (7H, m), 1.39 (9H, s), 1.33-1.02 (8H, m), 0.83 (2H, m).

Preparation 8:

(3R)-6-Cyclohexyl-3-{3-[(methylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(methylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 7, 380mg, 1.00mmol) in dichloromethane (10ml) was treated with trifluoroacetic acid (5ml) and the mixture was stirred at room temperature for 3.5 hours. The solvent was removed under reduced pressure and the residue azeotroped with toluene (x2). The residue was dissolved in ethyl acetate and washed sequentially with a saturated aqueous solution of sodium citrate then brine. The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was crystallised from hexane to afford the title compound as a white solid (310mg).

MPt. : 83-86°C

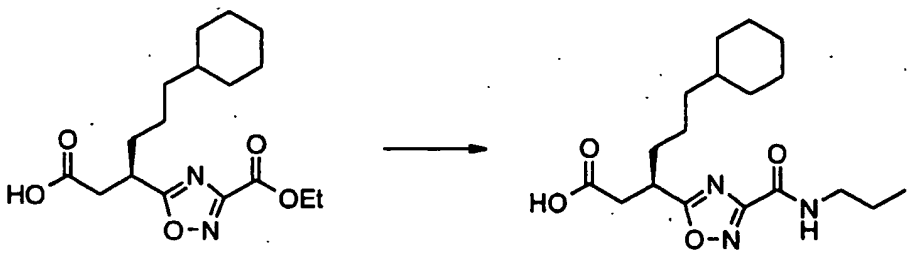
MS : 341 (MNH_4^+)

Analysis : Found C, 59.24; H, 7.75; N, 12.77%; $C_{16}H_{25}N_3O_4$ requires C, 59.43; H, 7.79; N, 12.79

^{1}H-NMR ($CDCl_3$) δ : 6.94 (1H, br m), 3.55 (1H, m), 3.01 (4H, m), 2.79 (1H, dd, J=14, 3), 1.86-1.53 (7H, m), 1.35-1.06 (8H, m), 0.83 (2H, m).

Preparation 9:

(3R)-6-Cyclohexyl-3-{3-[(propylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



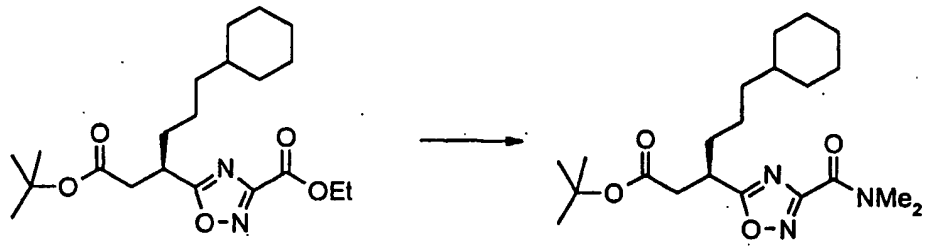
A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (107mg, 0.31mmol) in toluene (2ml) was treated with n-propylamine (250µl, 3.10mmol) and the mixture was heated at 125°C in a sealed vessel for 2 hours. The mixture was cooled to room temperature, diluted with ethyl acetate and washed sequentially with aqueous citric acid solution (5%w/v), water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (80 : 20) gradually changing to dichloromethane : ethyl acetate (60 : 40) then to dichloromethane : methanol (90 : 10) to afford the title compound as an oil (76mg).

MS : 352 (MH^+)

^{1}H-NMR (DMSO-d_6) δ : 8.90 (1H, m), 3.64-3.00 (3H, m), 2.80 (2H, m), 1.81-1.43 (9H, m), 1.39-1.00 (8H, m), 0.83 (5H, m).

Preparation 10:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(dimethylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (1.00g, 2.53mmol) in ethanol (8ml) was cooled to 0°C and treated dropwise with dimethylamine (5.6M in ethanol, 4.50ml, 25.3mmol). The solution was stirred for

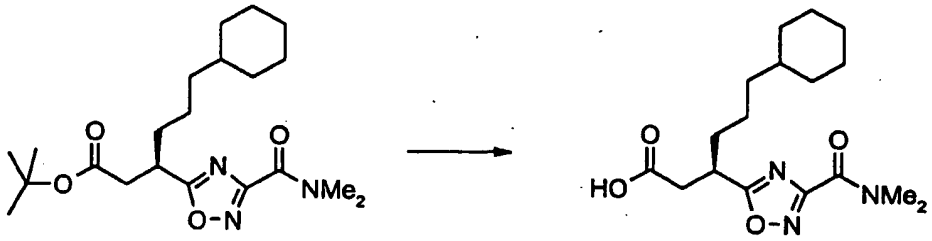
17 hours being allowed to warm up to room temperature over this time. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (4 : 1) to afford the title compound as a yellow oil (0.93g).

MS : 394 (MH^+), 411 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.50 (1H, m), 3.12 (6H, d), 2.85 (1H, dd, J=16, 7Hz), 2.65 (1H, dd, J=16, 5Hz), 1.84-1.57 (7H, m), 1.39 (9H, s), 1.34-1.05 (8H, m), 0.83 (2H, m).

Preparation 11:

(3R)-6-Cyclohexyl-3-{3-[(dimethylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(dimethylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 10) (2.35g, 5.97mmol) in dichloromethane (10ml) was treated with trifluoroacetic acid (2ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (98 : 2) to afford the title compound (1.27g).

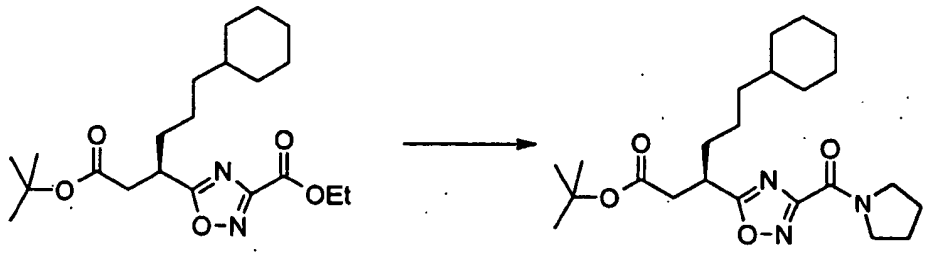
MS : 360 (MNa^+), 355 (MNH_4^+)

Analysis : Found C, 60.63; H, 8.16; N, 12.30%; $C_{17}H_{27}N_3O_4$ requires C, 60.51; H, 8.07; N, 12.45%

^{1}H-NMR (DMSO-d_6) δ : 3.45 (1H, m), 2.99 (3H, s), 3.91 (3H, s), 2.76 (2H, m), 1.73-1.52 (7H, m), 1.30-1.02 (8H, m), 0.80 (2H, m).

Preparation 12:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(1-pyrrolidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate



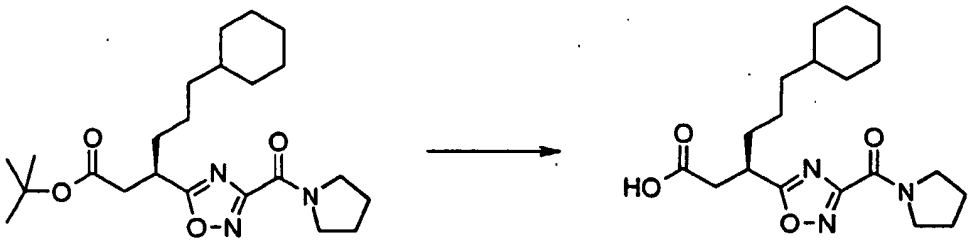
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated dropwise with pyrrolidine (0.63ml, 7.60mmol) and the resulting solution was heated at 60°C for 9 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (4 : 1) to afford the title compound as a pale yellow oil (360mg).

MS : 420 (MH^+), 437 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.71 (4H, m), 3.50 (1H, m), 2.86 (1H, dd, J=16, 8Hz), 2.64 (1H, dd, J=16, 3Hz), 1.96 (4H, m), 1.74-1.55 (7H, m), 1.38 (9H, s), 1.33-1.04 (8H, m), 0.82 (2H, m).

Preparation 13:

(3R)-6-Cyclohexyl-3-[3-(1-pyrrolidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



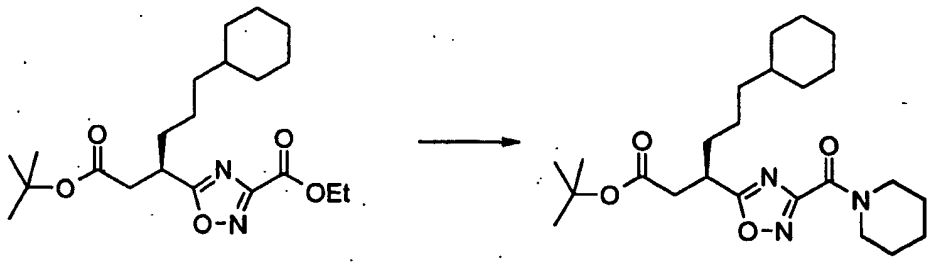
A solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(1-pyrrolidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 12) (356mg, 0.85mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (288mg).

MS : 364 (MH^+), 381 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 3.83-3.45 (5H, m), 2.94 (1H, dd, J=16, 8Hz), 2.81 (1H, dd, J=16, 4Hz), 1.98 (4H, m), 1.87-1.54 (7H, m), 1.44-1.06 (8H, m), 0.88 (2H, m).

Preparation 14:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(1-piperidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate



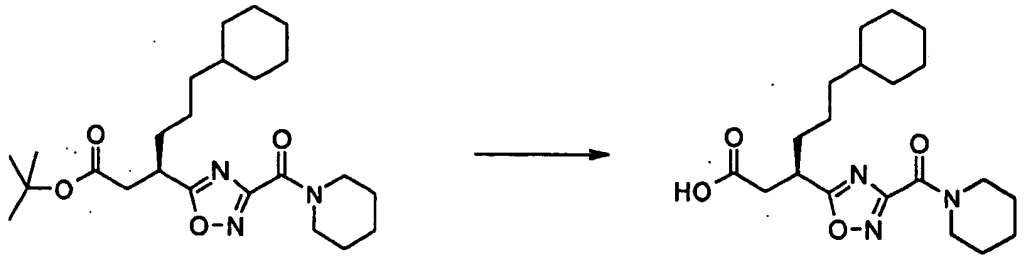
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated dropwise with piperidine (0.75ml, 7.60mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 9 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (80 : 20) to afford the title compound as a pale yellow oil (334mg).

MS : 434 (MH^+), 451(MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.72 (2H, m), 3.48 (3H, m), 2.84 (1H, dd, J=14, 8Hz), 2.65 (1H, dd, J=14, 4Hz), 1.86-1.53 (13H, m), 1.39 (9H, s), 1.33-1.05 (8H, m), 0.82 (2H, m).

Preparation 15:

(3R)-6-Cyclohexyl-3-[3-(1-piperidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(1-piperidinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 14) (334mg, 0.77mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound as a beige solid (266mg).

MS : 378 (MH^+), 395 (MNH_4^+)

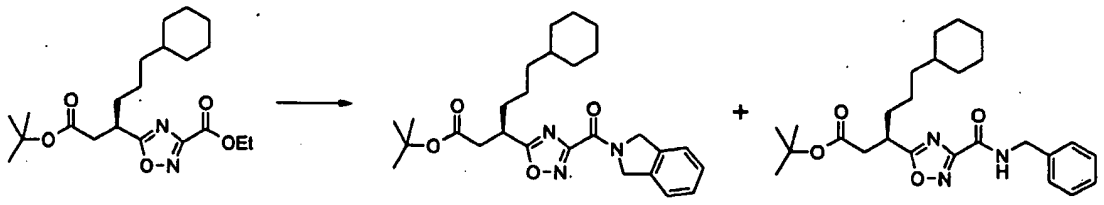
^{1}H-NMR (CD_3OD) δ : 3.73 (2H, m), 3.55 (1H, m), 3.43 (2H, m), 2.97-2.75 (2H, m), 1.86-1.57 (13H, m), 1.40-1.07 (8H, m), 0.87 (2H, m).

Preparation 16a :

tert-Butyl (3R)-6-cyclohexyl-3-[3-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate

Preparation 16b :

tert-Butyl (3R)-3-{3-[(benzylamino)carbonyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated with isoindoline hydrochloride (0.59g, 3.80mmol) (which also contained benzylamine) and triethylamine (0.74ml, 5.32mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 16 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (90 : 10). The

residue was further purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (99 : 1) to afford the title compound 16a (91mg).

MS : 468 (MH^+), 485 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 7.33 (4H, m), 5.19 (2H, s), 5.04 (2H, s), 3.56 (1H, m), 2.92 (1H, dd, J=15, 7Hz), 2.71 (1H, dd, J=15, 3Hz), 1.90-1.58 (7H, m), 1.41 (9H, s), 1.38-1.05 (8H, m), 0.83 (2H, m).

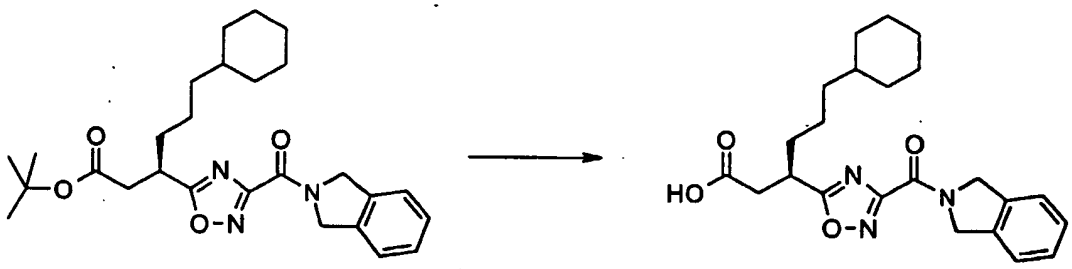
Further elution with dichloromethane : ethyl acetate (95 : 5) then gave compound 16b (173mg)

MS : 473 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 7.41-7.17 (5H, m), 4.66 (2H, d, J=5Hz), 3.50 (1H, m), 2.84 (1H, dd, J=15, 8Hz), 2.65 (1H, dd, J=15, 3Hz), 1.83-1.57 (7H, m), 1.39 (9H, s), 1.34-1.04 (8H, m), 0.83 (2H, m).

Preparation 17:

(3R)-6-Cyclohexyl-3-[3-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



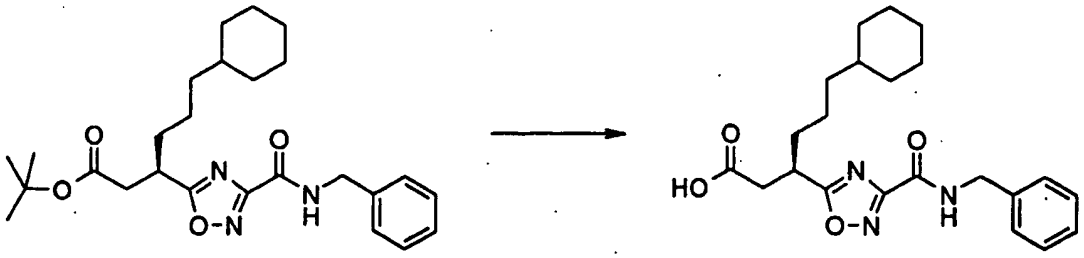
A solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 16a) (91mg, 0.19mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound as a beige solid (82mg).

MS : 412 (MH^+), 429 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 7.46-7.25 (4H, m), 5.19 (2H, s), 4.99 (2H, s), 3.62 (1H, m), 2.98 (1H, dd, J=17, 9Hz), 2.84 (1H, dd, J=17, 5Hz), 2.94-2.77 (7H, m), 1.47-1.06 (8H, m), 0.90 (2H, m).

Preparation 18 :

(3R)-3-{3-[(Benzylamino)carbonyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid



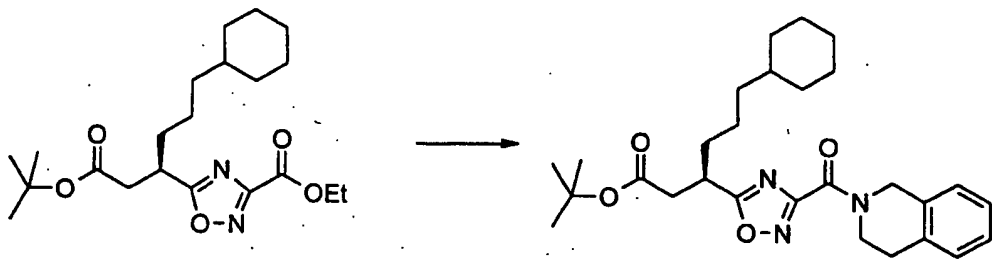
A solution of tert-butyl (3R)-3-{3-[(benzylamino)carbonyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate (Preparation 16b) (173mg, 0.38mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound as a beige solid (155mg).

MS : 400 (MH^+), 417 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 7.40-7.20 (5H, m), 4.56 (2H, s), 3.54 (1H, m), 2.93 (1H, dd, J=16, 8Hz), 2.80 (1H, dd, J=16, 3Hz), 1.83-1.67 (7H, m), 1.40-1.06 (8H, m), 0.86 (2H, m).

Preparation 19:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[3,4-dihydro-2(1H)-isoquinolinylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoate



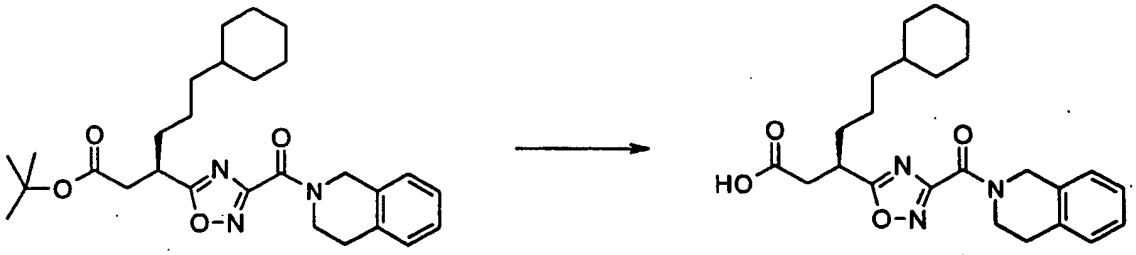
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated with 1,2,3,4-tetrahydroisoquinoline (0.95ml, 7.60mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 9 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (80 : 20). The residue was further purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (90 : 10) gradually changing to pentane : ethyl acetate (70 : 30) to afford the title compound (343mg).

MS : 482 (MH^+), 499 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 7.26-6.97 (4H, m), 4.92 (1.2H, s), 4.80 (0.8H, s), 4.00 (0.8H, m), 3.82 (1.2H, m), 3.53 (1H, m), 3.01-2.83 (3H, m), 2.67 (1H, dd, J=15, 3Hz), 1.87-1.58 (7H, m), 1.40 (9H, s), 1.36-1.08 (8H, m), 0.83 (2H, m)

Preparation 20:

(3R)-6-Cyclohexyl-3-{3-[3,4-dihydro-2(1H)-isoquinolinylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



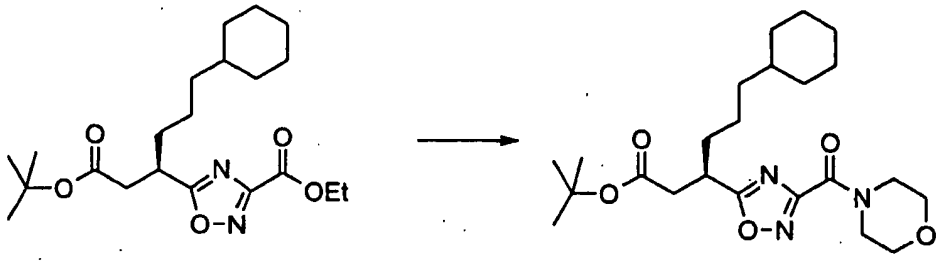
A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[3,4-dihydro-2(1H)-isoquinolinylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 19) (343mg, 0.71mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (281mg).

MS : 426 (MH^+), 443 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : (mixture of rotamers) 7.28-7.00 (4H, m), 4.87 (1.2H, s), 4.74 (0.8H, s), 3.99 (0.8H, m), 3.78 (1.2H, m), 3.57 (1H, m), 3.05-2.78 (4H, m), 1.86-1.57 (7H, m), 1.45-1.08 (8H, m), 0.87 (2H, m)

Preparation 21:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(4-morpholinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate



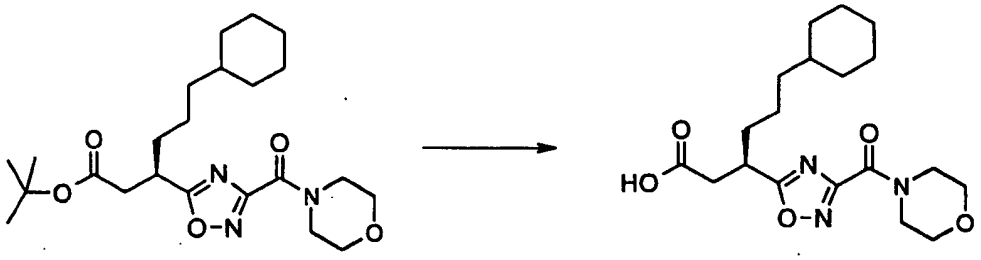
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was cooled to 0°C then treated with morpholine (0.066ml, 7.60mmol). The resulting mixture was warmed to room temperature and stirred under a nitrogen atmosphere for 17 hours. Further morpholine (0.53ml, 6.08mmol) was added and the mixture heated to 60°C for 8 hours. The mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : ethyl acetate (80 : 20) to afford title compound as a yellow oil (269mg)

MS : 436 (MH^+), 453 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.80 (4H, m), 3.67 (4H, m), 3.49 (1H, m), 2.84 (2H, dd, J=14, 8Hz), 2.65 (1H, dd, J=14, 3Hz), 1.84-1.57 (7H, m), 1.39 (9H, s), 1.33-1.06 (8H, m), 0.81 (2H, m)

Preparation 22:

(3R)-6-Cyclohexyl-3-[3-(4-morpholinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



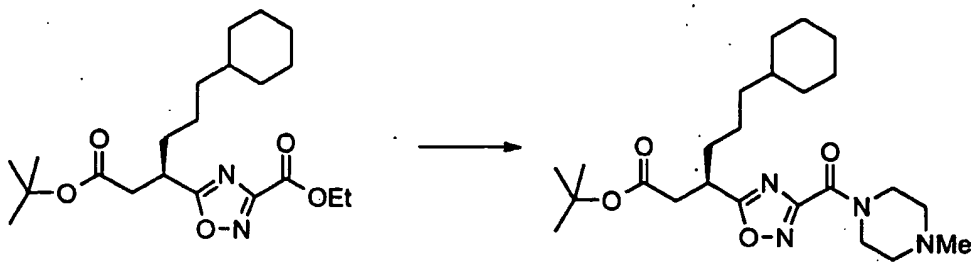
A solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(4-morpholinylcarbonyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 21) (269mg, 0.62mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (219mg).

MS : 380 (MH^+), 397 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.80 (4H, m), 3.68 (4H, m), 3.54 (1H, m), 3.00 (1H, dd, J=14, 8Hz), 2.78 (1H, dd, J=14, 3Hz), 1.88-1.57 (7H, m), 1.40-1.04 (8H, m), 0.85 (2H, m)

Preparation 23:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(4-methyl-1-piperazinyl)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate



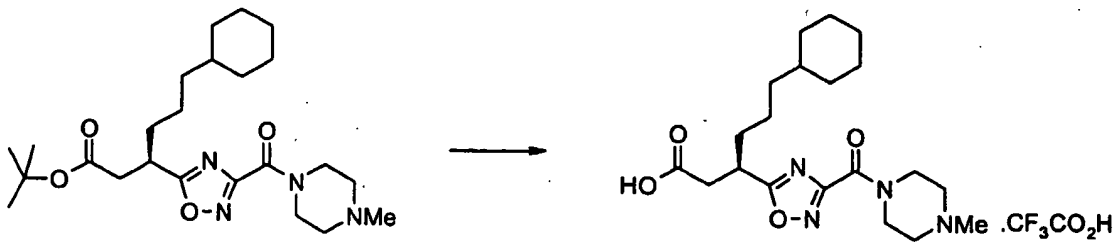
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated with 1-methylpiperazine (0.84ml, 7.60mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 16 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (98 : 2) gradually changing to dichloromethane : methanol (95 : 5) to afford the title compound (312mg).

MS : 449 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.80 (2H, m), 3.59 (2H, m), 3.47 (1H, m), 2.85 (1H, m), 2.65 (1H, m), 2.54-2.36 (4H, m), 2.30 (3H, s), 1.85-1.54 (7H, m), 1.37 (9H, s), 1.33-1.04 (8H, m), 0.81 (2H, m)

Preparation 24:

(3R)-6-Cyclohexyl-3-{3-[(4-methyl-1-piperazinyl)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid trifluoroacetate



A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(4-methyl-1-piperazinyl)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 23) (312mg, 0.70mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a

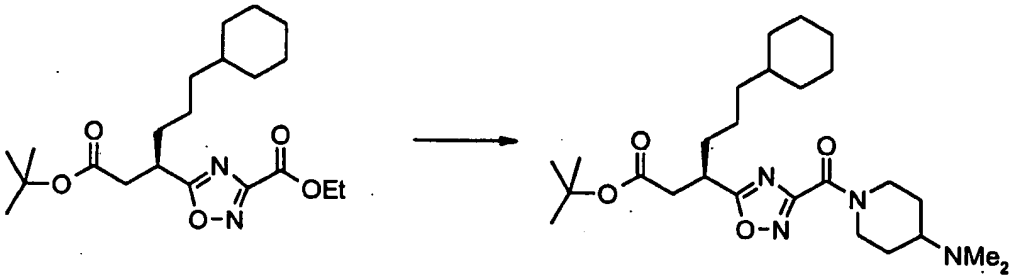
nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound as a white foam (320mg).

MS : 393 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.03 (4H, br m), 3.56 (1H, m), 3.41 (4H, m), 2.98-2.78 (5H, m), 1.83 (7H, m), 1.40-1.12 (8H, m), 0.87 (2H, m)

Preparation 25:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



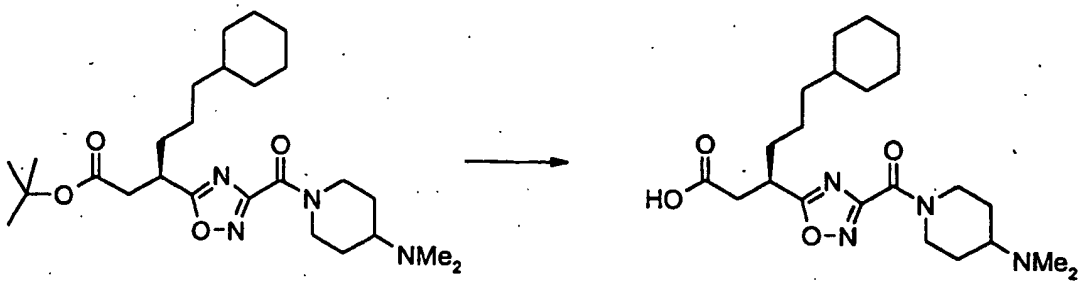
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (800mg, 2.03mmol) in ethanol (10ml) was treated with N,N-dimethyl-N-(4-piperidinyl)amine (1.23g, 9.61mmol) and the resulting mixture was heated under reflux under a nitrogen atmosphere for 3 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed sequentially with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (90 : 10) to give a residue which was further purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (90 : 10 : 0.5) to afford the title compound as a yellow oil (653mg).

MS: 477 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.77 (1H, m), 4.05 (1H, m), 3.50 (1H, m), 3.13 (1H, m), 2.92-2.60 (4H, m), 2.40 (6H, s), 2.04-1.50 (9H, m), 1.40 (9H, s), 1.36-1.07 (10H, m), 0.84 (2H, m)

Preparation 26:

(3R)-6-Cyclohexyl-3-(3-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid trifluoroacetate



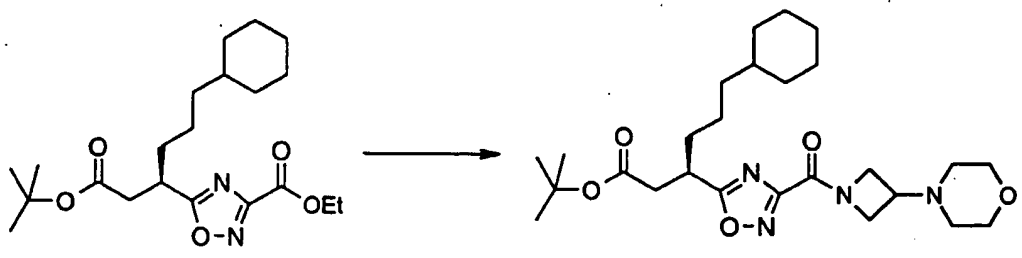
A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[4-(dimethylamino)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 25) (652mg, 1.37mmol) in dichloromethane (15ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The resulting mixture was stirred for 2 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue azeotroped from toluene. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol : 0.88 ammonia (90 : 10 : 1) gradually changing to dichloromethane : methanol : 0.88 ammonia (70 : 30 : 2) to afford the title compound as a colourless oil (702mg).

MS: 421 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.80 (1H, m), 4.09 (1H, m), 3.55 (1H, m), 3.22 (2H, m), 2.93 (1H, m), 2.83-2.60 (8H, m), 2.20-2.00 (2H, m), 1.82-1.54 (9H, m), 1.41-1.07 (8H, m), 0.87 (2H, m)

Preparation 27:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[3-(4-morpholinyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (1.00g, 2.54mmol) in ethanol (10ml) was treated with 4-(3-

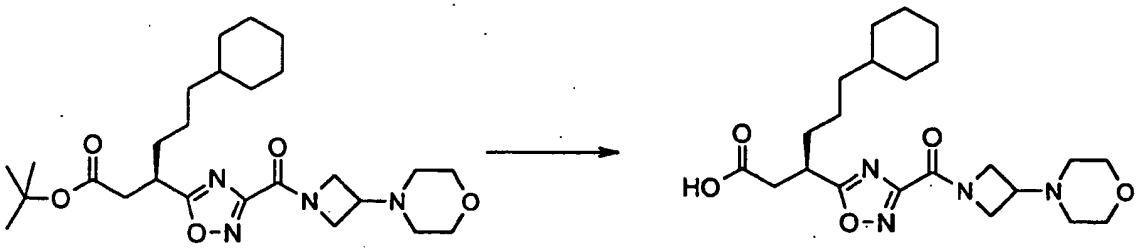
azetidinyl)morpholine dihydrochloride (2.72g, 12.6mmol) and triethylamine (2.56g, 25mmol) and the resulting mixture was heated under reflux under a nitrogen atmosphere for 24 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed sequentially with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (97 : 3) gradually changing to dichloromethane : methanol (95 : 5) to afford the title compound as a colourless oil (1.32g).

MS: 491 (MH^+), 508 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : 4.64 (1H, m), 4.43 (1H, m), 4.25 (1H, m), 4.05 (1H, m), 3.73 (4H, m), 3.52 (1H, m), 3.31 (1H, m), 2.84-2.66 (2H, m), 2.45 (4H, m), 1.85-1.55 (7H, m), 1.46-1.05 (17H, m), 0.86 (2H, m)

Preparation 28:

(3R)-6-Cyclohexyl-3-(3-{[3-(4-morpholinyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid trifluoroacetate



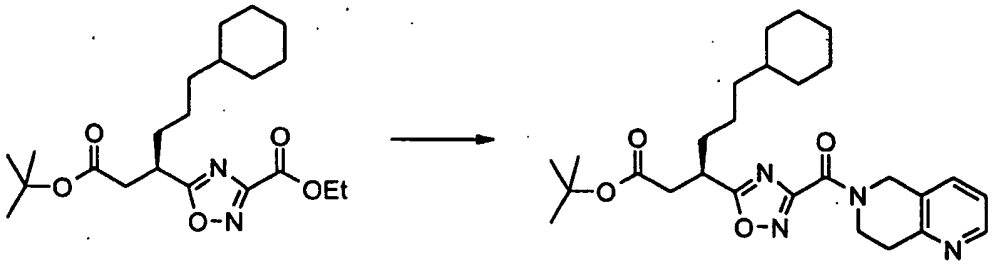
A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[3-(4-morpholinyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 27) (1.32g, 2.70mmol) in dichloromethane (15ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The resulting mixture was stirred for 3 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x3) then dichloromethane to afford the title compound as a white foam (1.31g).

MS: 435 (MH^+)

^{1}H-NMR (CD_3OD) δ : 4.86 (1H, m), 4.50 (1H, m), 4.39 (1H, m), 4.14 (1H, m), 3.92 (4H, m), 3.56 (1H, m), 3.37-3.17 (5H, m), 2.93 (1H, dd, J=13, 8Hz), 2.82 (1H, dd, J=13, 3Hz), 1.83-1.59 (7H, m), 1.39-1.09 (8H, m), 0.86 (2H, m)

Preparation 29:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[7,8-dihydro[1,6]naphthyridin-6(5H)-ylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoate



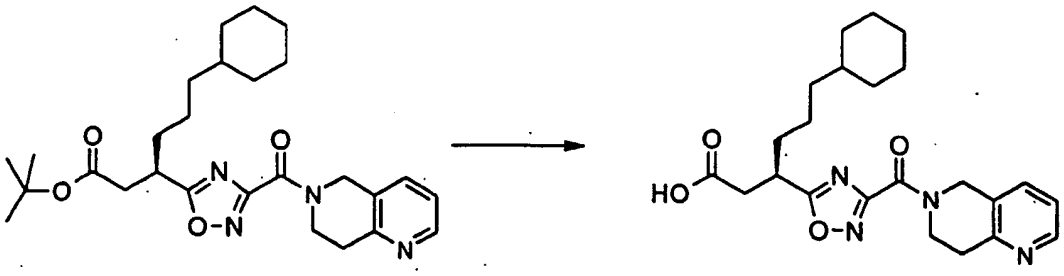
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated with 5,6,7,8-tetrahydro[1,6]naphthyridine dihydrochloride (Chem.Pharm.Bull.; 32; 7; 1984; 2522-2529) (0.79g, 3.80mmol) and triethylamine (1.27ml, 9.13mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 16 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (90 : 10) gradually changing to dichloromethane : ethyl acetate (50 : 50) to afford the title compound (281mg).

MS : 483 (MH^+), 505 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 8.44 (1H, d, J=3Hz), 7.48 (0.67H, d, J=6Hz), 7.33 (0.33H, d, J=6Hz), 7.20-7.10 (1H, m), 4.92 (1.34H, s), 4.83 (0.66H, s), 4.13 (0.66H, t, J=5Hz), 3.94 (1.34H, t, J=5Hz), 3.52 (1H, m), 3.13 (2H, m), 2.87 (1H, dd, J=14, 7Hz), 2.67 (1H, dd, J=14, 3Hz), 1.85-1.56 (7H, m), 1.39 (9H, d), 1.35-1.04 (8H, m), 0.83 (2H, m)

Preparation 30:

(3R)-6-Cyclohexyl-3-{3-[7,8-dihydro[1,6]naphthyridin-6(5H)-ylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoic acid trifluoroacetate



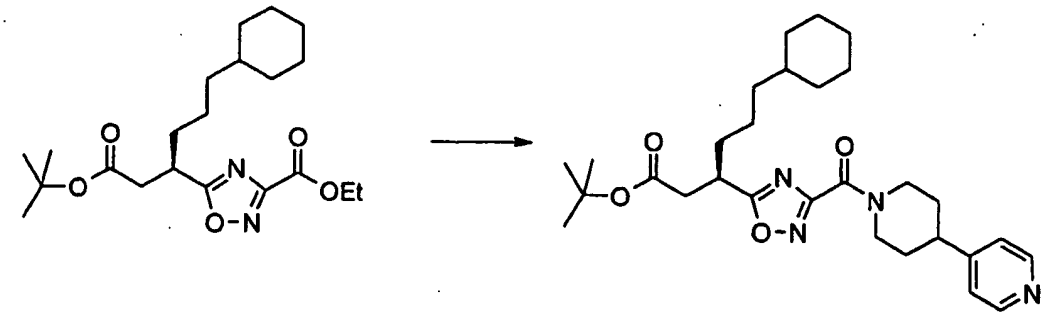
A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[7,8-dihydro[1,6]naphthyridin-6(5H)-ylcarbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 29) (281mg, 0.58mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (245mg).

MS : 427 (MH^+)

^{1}H-NMR (CD_3OD) δ : (mixture of rotamers) 8.56 (1H, d, 5Hz), 8.17 (0.67H, d, J=8Hz), 8.01 (0.33H, d, J=8Hz), 7.73-7.56 (1H, m), 5.05 (1.34H, s), 5.00 (0.66H, s), 4.16 (0.66H, m), 4.01 (1.34H, m), 3.59 (1H, m), 3.24 (2H, m), 3.04-2.76 (2H, m), 1.92-1.55 (7H, m), 1.46-1.06 (8H, m), 0.87 (2H, m)

Preparation 31:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[4-(4-pyridinyl)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (0.50g, 1.27mmol) in ethanol (10ml) was treated with 4-(4-pyridinyl)piperidine (Monatsh.Chem.; 3; 1882; 867) (0.41g, 2.54mmol) and the resulting mixture was heated under reflux under a nitrogen atmosphere for 72 hours. Further 4-(4-

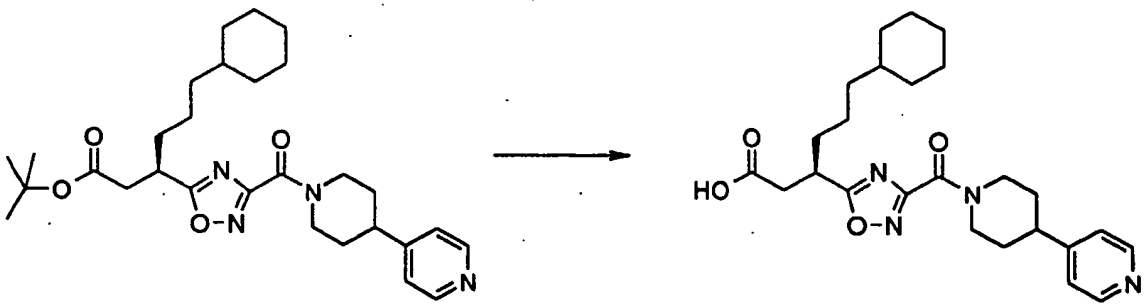
pyridinyl)piperidine (0.21g, 1.27mmol) was added and the mixture heated under reflux for 24 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed sequentially with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (95 : 5) to afford the title compound as a pale yellow oil (0.39g).

MS: 511 (MH^+)

^{1}H-NMR (CD_3OD) δ : 8.44 (2H, d, J=4Hz), 7.35 (2H, d, J=4Hz), 4.79 (1H, m), 4.00 (1H, m), 3.53 (1H, m), 3.34 (1H, m), 3.00 (2H, m), 2.84 (1H, dd, J=14, 8Hz), 2.75 (1H, dd, 14, 5Hz), 2.02 (1H, m), 1.92 (1H, m), 1.83-1.58 (9H, m), 1.44-1.09 (17H, m), 0.86 (2H, m)

Preparation 32:

(3R)-6-Cyclohexyl-3-(3-{[4-(4-pyridinyl)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[4-(4-pyridinyl)-1-piperidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 31) (376mg, 0.74mmol) in dichloromethane (15ml) was cooled to 0°C and treated with trifluoroacetic acid (5ml). The resulting mixture was stirred for 3 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x3) then dichloromethane. A saturated solution of sodium carbonate was added to the residue until a pH of 12 was achieved followed by dropwise addition of an aqueous citric acid solution solution (10% w/v) until the pH became 3.5. The solution was then diluted with water and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered

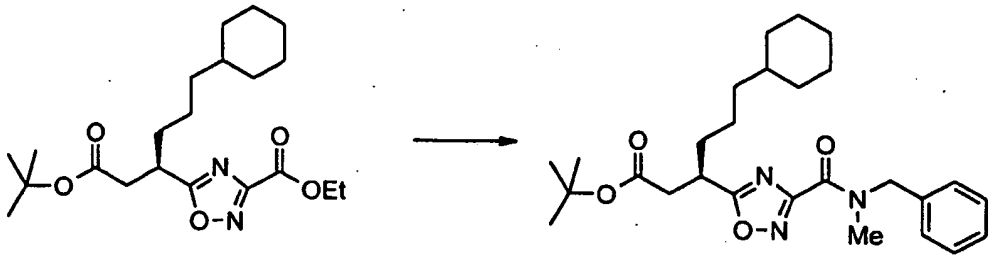
and the solvent removed under reduced pressure to afford the title compound as a white solid (310mg).

MS: 455 (MH^+)

^{1}H-NMR (CD_3OD) δ : 8.44 (2H, d, J=4Hz), 7.36 (2H, d, J=4Hz), 4.78 (1H, m), 3.97 (1H, m), 3.56 (1H, m), 3.34 (1H, m), 3.06-2.75 (4H, m), 2.01 (1H, m), 1.92 (1H, m), 1.83-1.56 (9H, m), 1.40-1.04 (8H, m), 0.85 (2H, m)

Preparation 33:

tert-Butyl (3R)-3-(3-{[benzyl(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)-6-cyclohexylhexanoate



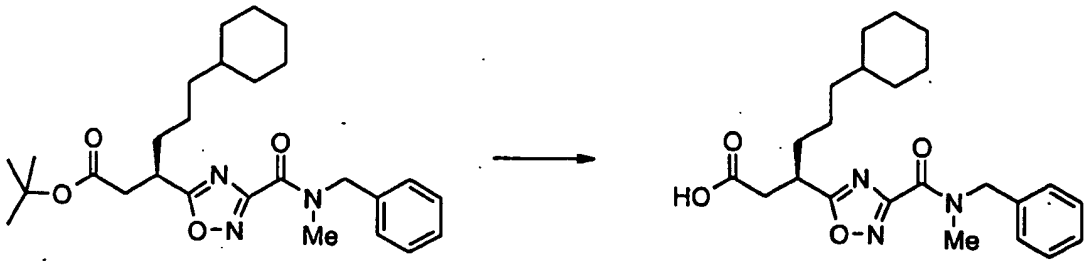
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (300mg, 0.76mmol) in ethanol (4ml) was treated with N-benzyl-N-methylamine (0.98ml, 7.60mmol) and the resulting mixture was heated at 60°C under a nitrogen atmosphere for 16 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (100 : 0) gradually changing to dichloromethane : ethyl acetate (95 : 5) to afford the title compound (296mg).

MS : 470 (MH^+), 487 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : (mixture of rotamers) 7.42-7.21 (5H, m), 4.79 (1H, d, J=15Hz), 4.63 (1H, d, J=15Hz), 3.52 (1H, m), 3.00 (3H, m), 2.90-2.67 (2H, m), 1.85-1.57 (7H, m), 1.41-1.04 (17H, m), 0.84 (2H, m)

Preparation 34:

(3R)-3-(3-{[Benzyl(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)-6-cyclohexylhexanoic acid



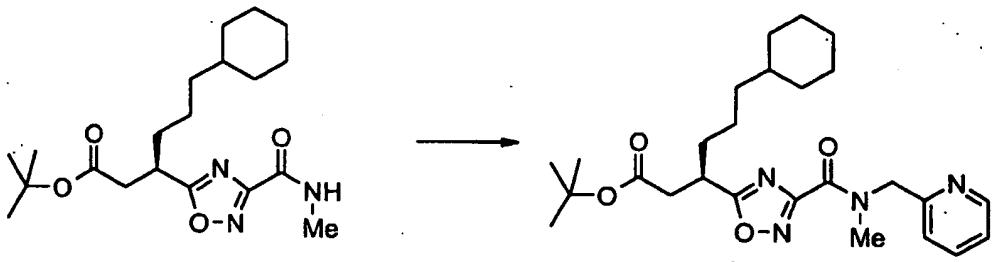
A solution of tert-butyl (3R)-3-(3-{[benzyl(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)-6-cyclohexylhexanoate (Preparation 33) (296mg, 0.63mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (226mg).

MS : 414 (MH^+), 431 (MNH_4^+)

^{1}H-NMR (CD_3OD) δ : (mixture of rotamers) 7.42-7.22 (5H, m), 4.79 (1H, d, J=15Hz), 4.58 (1H, d, 15Hz), 3.56 (1H, m), 3.00 (3H, d), 2.97-2.73 (2H, m), 1.84-1.55 (7H, m), 1.41-1.03 (8H, m), 0.83 (2H, m)

Preparation 35:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[methyl(2-pyridinylmethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



1-1'-Azobis(N,N-dimethylformamide) (645mg, 3.75mmol) was added to a cooled solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(methylamino)carbonyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 7) (1.42g, 3.75mmol), tributylphosphine (930µl, 3.75mmol) and 2-hydroxymethylpyridine (240µl, 2.50mmol) in toluene (10ml) and the resulting mixture was stirred at 0°C under a nitrogen atmosphere for 15 minutes, then at room temperature for 72 hours. The mixture was filtered and the solvent removed from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of

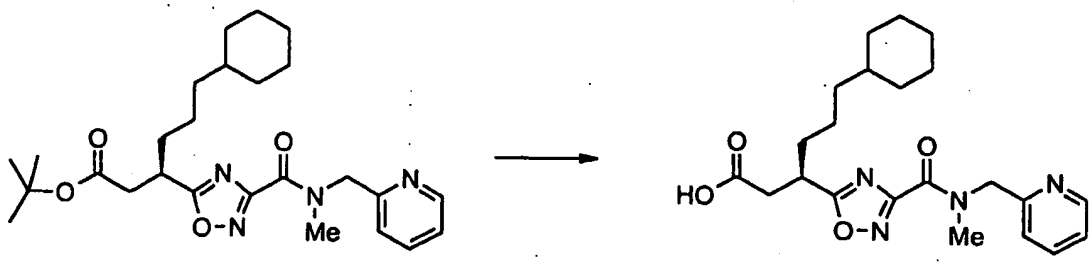
hexane : ethyl acetate (90 : 10) gradually changing to hexane : ethyl acetate (50 : 50) to afford the title compound as a pale yellow oil (530mg).

MS : 472 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 8.54 (1H, m), 7.68 (1H, m), 7.44-7.15 (2H, m), 4.86 (1H, s), 4.79 (1H, s), 3.51 (1H, m), 3.16 (1.5H, s), 3.10 (1.5H, s), 2.84 (1H, m), 2.63 (1H, m), 1.89-1.52 (7H, m), 1.36 (9H, d), 1.31-1.00 (8H, m), 0.81 (2H, m)

Preparation 36:

(3R)-6-Cyclohexyl-3-(3-{[methyl(2-pyridinylmethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



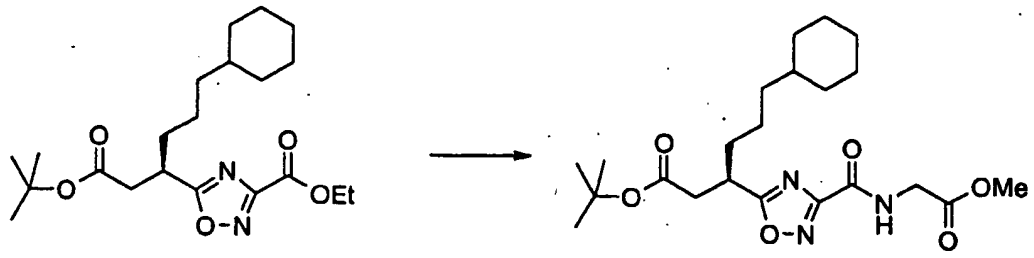
A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[methyl(2-pyridinylmethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 35) (527mg, 1.12mmol) in dichloromethane (20ml) was treated with trifluoroacetic acid (10ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours. The solvent was removed under reduced pressure and the residue was azeotroped from toluene. The residue was dissolved in a saturated aqueous solution of sodium hydrogen carbonate (3ml) and the pH was adjusted to pH 4 with aqueous citric acid solution (10%w/v). The aqueous phase was extracted with ethyl acetate (x2) and the combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a yellow oil (456mg)

MS : 414 (M^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 8.51 (1H, m), 7.75 (1H, m), 7.47 (0.5H, d, J=6Hz), 7.40 (0.5H, d, J=6Hz), 7.23 (1H, m), 4.96-4.66 (2H, m), 3.51 (1H, m), 3.10 (3H, d), 3.05-2.66 (2H, m), 1.89-1.52 (7H, m), 1.40-1.01 (8H, m), 0.82 (2H, m)

Preparation 37:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



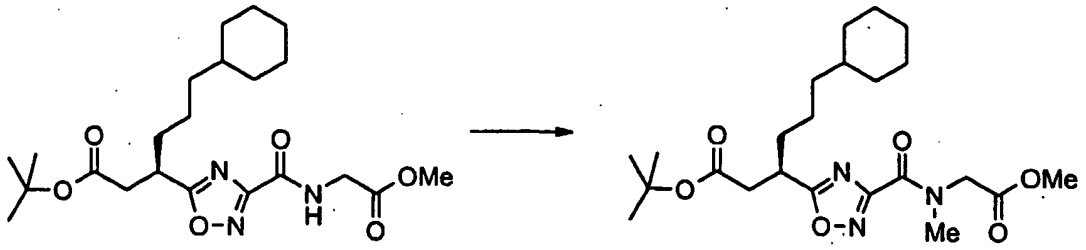
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (1.18g, 3.00mmol) and triethylamine (1.51g, 15.00mmol) in ethanol (30ml) was treated with glycine methyl ester hydrochloride (1.88g, 15.00mmol) and the resulting mixture was heated at 80°C under a nitrogen atmosphere for 16 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane : ethyl acetate (90 : 10) gradually changing to hexane : ethyl acetate (50 : 50) to afford the title compound (456mg).

MS : 455 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 7.42 (1H, br t), 4.25 (2H, d, J=4Hz), 3.80 (3H, s), 3.51 (1H, m), 2.84 (1H, dd, J=14, 9Hz), 2.66 (1H, dd, J=14, 3Hz), 1.83-1.55 (7H, m), 1.38 (9H, s), 1.34-1.07 (8H, m), 0.84 (2H, m)

Preparation 38:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



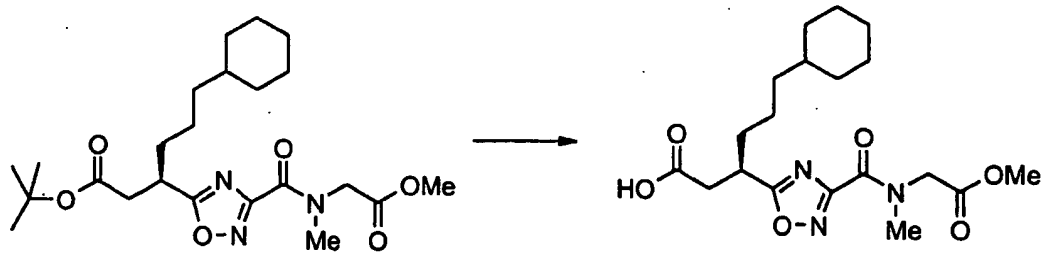
A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 37) (440mg, 1.00mmol) in anhydrous dimethylsulphoxide (10ml) was treated with iodomethane (310µl, 5.00mmol) and cesium carbonate (975mg, 3.00mmol) and the resulting mixture was heated at 40° under a nitrogen atmosphere for 3 hours then stirred at room temperature for 17 hours. The mixture was diluted with water and extracted with diethyl ether (x3). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane : ethyl acetate (2 : 1) to afford the title compound as a colourless oil (315mg)

MS : 452 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 4.36 (1H, s), 4.30 (1H, s), 3.76 (3H, d), 3.51 (1H, m), 3.25 (1.5H, s), 3.20 (1.5H, s), 2.86 (1H, m), 2.66 (1H, m), 1.85-1.57 (7H, m), 1.39 (9H, s), 1.34-1.04 (8H, m), 0.84 (2H, m)

Preparation 39:

(3R)-6-Cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 38) (315mg, 0.70mmol) in dichloromethane (10ml) was treated with trifluoroacetic acid (5ml) and the resulting mixture was stirred at room

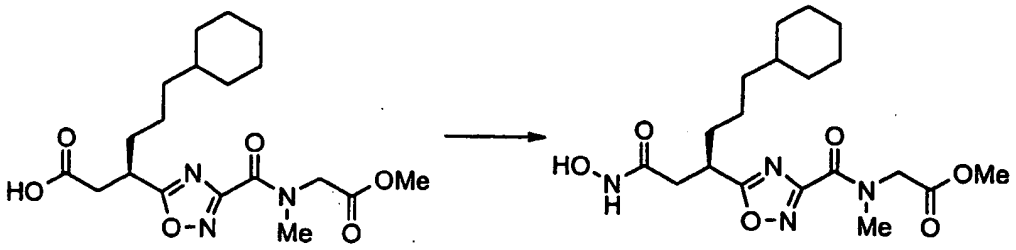
temperature under a nitrogen atmosphere for 2 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium citrate and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil (273mg)

MS : 396 (MH^+), 418 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 4.26 (1.6H, m), 4.11 (0.4H, m), 3.75 (3H, d), 3.52 (1H, m), 3.21 (3H, d), 3.00 (1H, m), 2.78 (1H, m), 1.89-1.41 (7H, m), 1.38-0.95 (8H, m), 0.80 (2H, m)

Preparation 40/Example 41:

Methyl 2-[[(5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazol-3-yl)carbonyl](methyl)amino]acetate



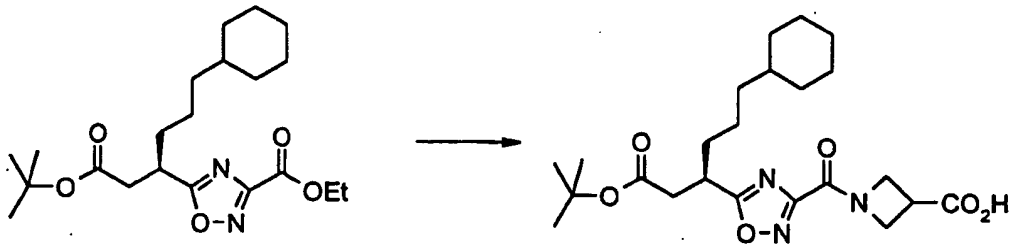
A solution of (3R)-6-cyclohexyl-3-(3-{[(2-methoxy-2-oxoethyl)(methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid (Preparation 39) (273mg, 0.70mmol)and N-methylmorpholine (85µl, 0.77mmol) in anhydrous dichloromethane (10ml) was cooled to 0°C, treated with isobutyl chloroformate (100µl, 0.77mmol) and the resulting mixture was stirred under a nitrogen atmosphere for 30 minutes. O-(Trimethylsilyl)hydroxylamine (250µl, 2.10mmol) was then added and the mixture stirred under a nitrogen atmosphere for 1 hour, being allowed to warm to room temperature over this time. The mixture was then quenched with methanol (10ml) and stirred for 10 minutes. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The layers were separated and the organic layer was sequentially washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by HPLC[a] to afford the title compound as a colourless oil (187mg).

MS : 411 (MH^+), 433 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : (mixture of rotamers) 4.50-4.21 (2H, m), 3.84-3.60 (4H, m), 3.32 (1.8H, s), 3.21 (1.2H, s), 2.81-2.56 (2H, m), 1.90-1.50 (7H, m), 1.40-1.03 (8H, m), 0.82 (2H, m)

Preparation 41:

1-[(5-{(1R)-1-[2-(tert-Butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylic acid

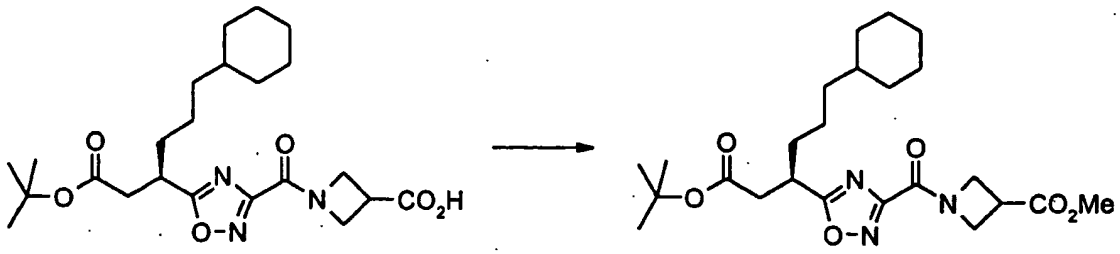


A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (790mg, 2.00mmol) in dimethylsulphoxide (25ml) was treated with 3-azetidine carboxylic acid (505mg, 5.00mmol) and potassium carbonate (690mg, 5.00mmol) and the resulting mixture was heated at 95°C under a nitrogen atmosphere for 16 hours. The mixture was cooled and the mixture treated with hydrochloric acid (1M, 25ml) then diluted further with water (25ml) and extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (90 : 10) to afford the title compound as a pale yellow oil (490mg).

^{1}H-NMR ($CDCl_3$) δ : 4.76 (2H, m), 4.45 (2H, m), 3.64-3.43 (2H, m), 2.89 (1H, dd, J=15, 8Hz), 2.65 (1H, dd, J=15, 4Hz), 1.84-1.56 (7H, m), 1.38 (9H, s), 1.34-1.03 (8H, m), 0.84 (2H, m)

Preparation 42:

Methyl 1-[(5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylate



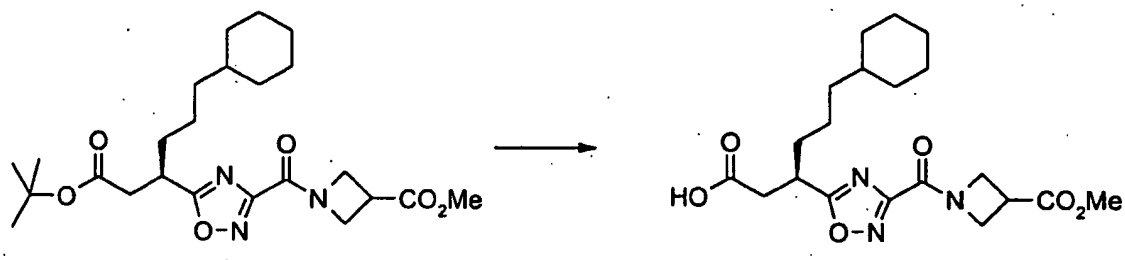
A solution of 1-[(5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylic acid (Preparation 41) (480mg, 1.07mmol) and N-methylmorpholine (130µl, 1.17mmol) in dichloromethane (10ml) was cooled to 0°C and then treated with isobutyl chloroformate (150µl, 1.17mmol). The mixture was stirred at 0°C for 30 minutes then allowed to warm to room temperature over 1 hour. The mixture was quenched with methanol (5ml) and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and hydrochloric acid (1M). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : ethyl acetate (95 : 5) gradually changing to dichloromethane : ethyl acetate (90 : 10) to afford the title compound (230mg)

MS : 464 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.73 (2H, m), 4.40 (2H, m), 3.78 (3H, s), 3.52 (2H, m), 2.86 (1H, dd, J=15, 8Hz), 2.64 (1H, dd, J=15, 3Hz), 1.83-1.58 (7H, m), 1.38 (9H, s), 1.33-1.06 (8H, m), 0.83 (2H, m)

Preparation 43:

(3R)-6-Cyclohexyl-3-(3-{[3-(methoxycarbonyl)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



A solution of methyl 1-[(5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazol-3-yl)carbonyl]-3-azetidinecarboxylate (Preparation 42) (225mg, 0.48mmol) in dichloromethane

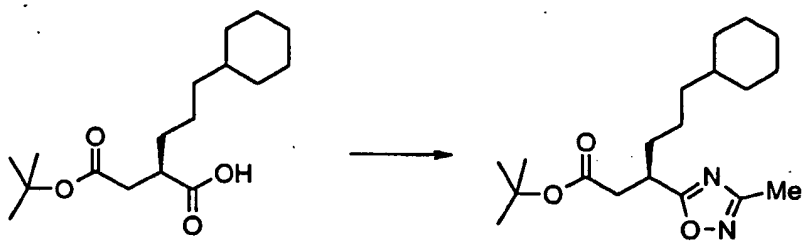
(8ml) was treated with trifluoroacetic acid (4ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 5 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene (x2). The residue was dissolved in ethyl acetate and washed sequentially with a saturated aqueous solution of sodium citrate and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as an oil (200mg).

MS : 408 (MH^+), 430 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.73 (2H, m), 4.40 (2H, m), 3.78 (3H, s), 3.53 (2H, m), 3.04 (1H, m), 2.80 (1H, m), 1.87-1.41 (7H, m), 1.36-1.00 (8H, m), 0.83 (2H, m)

Preparation 44:

tert-Butyl (3R)-6-cyclohexyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)hexanoate



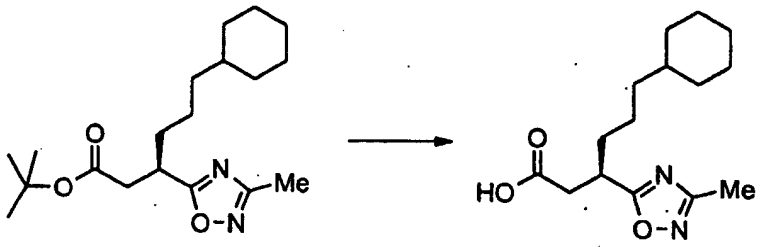
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (596mg, 2.00mmol) in dichloromethane (8ml) was treated with 1,1'-carbonyldiimidazole (364mg, 2.25mol) and the solution was stirred at room temperature for 15 minutes. The N-hydroxy-acetamidine (Chem.Ber.; 17; 1884; 2746) (148mg, 2.00mmol) was then added and the mixture was stirred for 1 hour. The solvent was removed under reduced pressure and the residue was heated neat under a nitrogen atmosphere for 90 minutes. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane to afford the title compound (385mg).

MS : 337 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.41 (1H, m), 2.76 (1H, dd, J=14, 8Hz), 2.60 (1H, dd, J=14, 5Hz), 2.36 (3H, s), 1.76-1.56 (7H, m), 1.39 (9H, s), 1.32-1.04 (8H, m), 0.82 (2H, m)

Preparation 45:

(3R)-6-Cyclohexyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)hexanoic acid



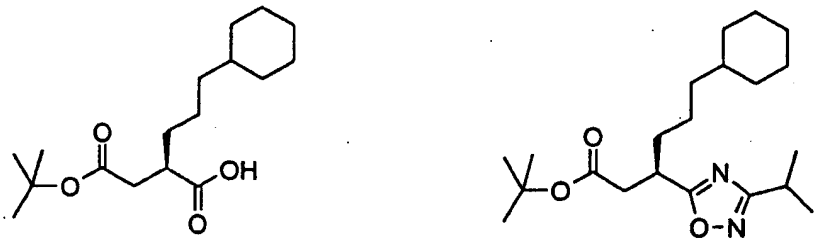
tert-Butyl (3R)-6-cyclohexyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 44) (350mg, 1.04mmol) was treated with trifluoroacetic acid (3ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 45 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound (185mg).

MS : 298 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 3.41 (1H, m), 2.96 (1H, dd, J=16, 8Hz), 2.75 (1H, dd, J=16, 6Hz), 2.36 (3H, s), 1.80-1.40 (7H, m), 1.35-0.93 (8H, m), 0.82 (2H, m)

Preparation 46:

tert-Butyl (3R)-6-cyclohexyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)hexanoate



A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.70mmol) in dichloromethane (30ml) was treated with 1,1'-carbonyldiimidazole (272mg, 1.70mol) and the solution was stirred at room temperature for 1 hour. The N'-hydroxy-2-methylpropanimidamide (Monatsh.Chem.; 113; 1982; 781-792) (174mg, 1.70mmol) was then added and the mixture was stirred for 30 minutes. The solvent was removed under reduced pressure and the residue was heated neat at 120°C under a nitrogen atmosphere for 18 hours.

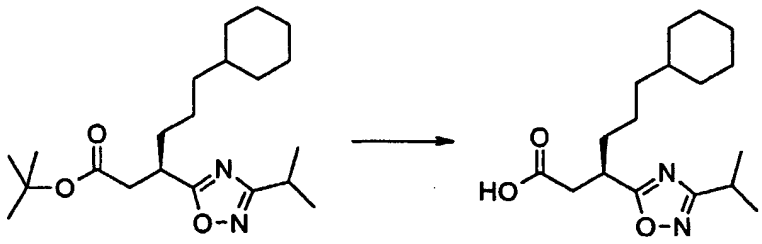
The crude product was then purified by column chromatography on silica gel eluting with dichloromethane to afford the title compound as a colourless oil (250mg).

MS : 365 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.42 (1H, m), 3.05 (1H, m), 2.78 (1H, dd, J=16, 8Hz), 2.60 (1H, dd, J=16, 4Hz), 1.70-1.57 (7H, m), 1.39 (9H, s), 1.34-1.06 (14H, m), 0.81 (2H, m)

Preparation 47:

(3R)-6-Cyclohexyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)hexanoic acid



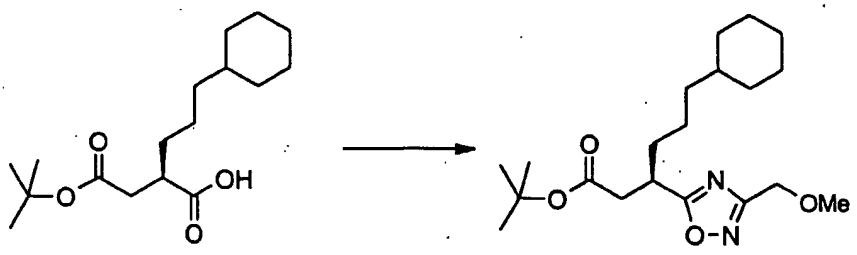
tert-Butyl (3R)-6-cyclohexyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 46) (250mg, 0.69mmol) was treated with trifluoroacetic acid (5ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 45 minutes. The solvent was removed under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound as a white solid (220mg).

MS : 309 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.50 (1H, m), 3.09 (1H, m), 2.95 (2H, dd, J=16, 8Hz), 2.76 (1H, dd, J=16, 4Hz), 1.84-1.56 (7H, m), 1.40-1.05 (14H, m), 0.81 (2H, m)

Preparation 48:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate



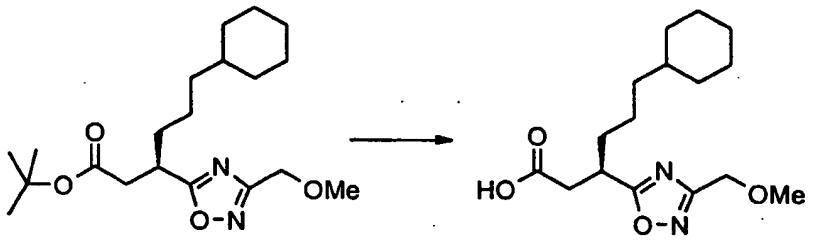
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.70mmol) in dichloromethane (30ml) was treated with 1,1'-carbonyldiimidazole (272mg, 1.70mol) and the solution was stirred at room temperature for 1 hour. The N'-hydroxy-2-methoxyethanimidamide (J.Med.Chem,; 40; 8; 1997; 1230-1246) (177mg, 1.70mmol) was then added and the mixture was stirred for 17 hours. The solvent was removed under reduced pressure and the residue was heated neat at 120°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1) to afford the title compound as an oil (350mg).

MS : 367 (MH^+), 389 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.56 (2H, s), 3.49 (4H, m), 2.84 (1H, dd, J=16, 8Hz), 2.65 (1H, dd, J=16, 5Hz), 1.85-1.52 (7H, m), 1.40 (9H, s), 1.36-1.05 (8H, m), 0.84 (2H, m)

Preparation 49:

(3R)-6-Cyclohexyl-3-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



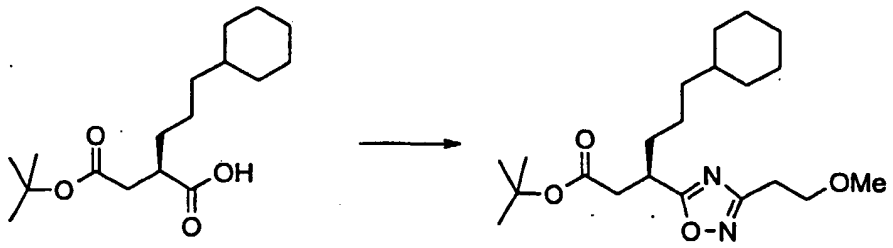
tert-Butyl (3R)-6-cyclohexyl-3-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 48) (350mg, 0.96mmol) was treated with trifluoroacetic acid (3ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound as a colourless oil (250mg).

MS : 311 (MH^+), 333 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.57 (2H, s), 3.50 (4H, m), 3.00 (1H, m), 2.89 (1H, m), 1.90-1.51 (7H, m), 1.40-1.01 (8H, m), 0.84 (2H, m)

Preparation 50:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl]hexanoate



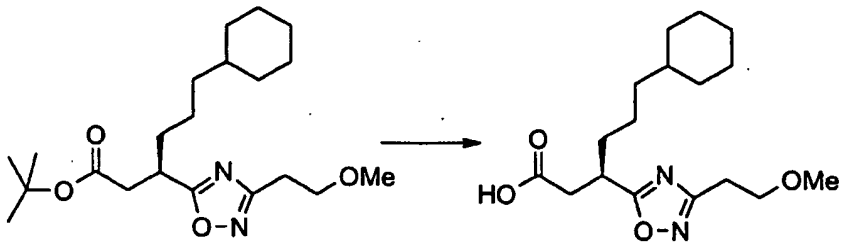
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.70mmol) in dichloromethane (30ml) was treated with 1,1'-carbonyldiimidazole (272mg, 1.70mmol) and the solution was stirred at room temperature for 1 hour. N'-hydroxy-3-methoxypropanimidamide (J.Amer.Chem.Soc.; 80; 1958; 3769-3771) (201mg, 1.70mmol) was then added and the mixture was stirred for 1 hour. The solvent was removed under reduced pressure and the residue was heated neat at 120°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1) to afford the title compound as a colourless oil (410mg).

MS : 381 (MH^+), 403 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 3.73 (2H, t, J=6Hz), 3.42 (1H, m), 3.34 (3H, s), 2.98 (2H, t, J=6Hz), 2.77 (1H, dd, J=16, 9Hz), 2.61 (1H, dd, J=16, 5Hz), 1.79-1.54 (7H, m), 1.38 (9H, s), 1.32-1.03 (8H, m), 0.81 (2H, m)

Preparation 51:

(3R)-6-Cyclohexyl-3-[3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



tert-Butyl (3R)-6-cyclohexyl-3-[3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 50) (410mg, 1.08mmol) was treated with trifluoroacetic acid (3ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour. The solvent was removed

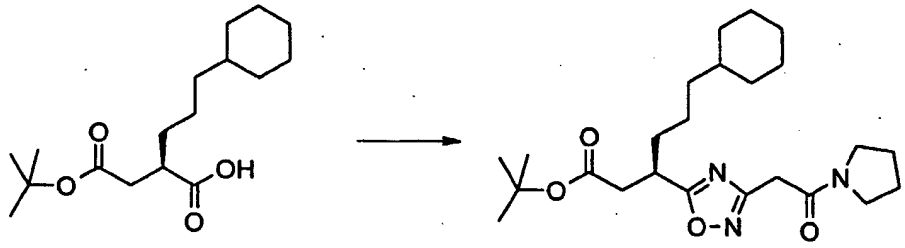
under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound (250mg).

MS : 325 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 7.46 (1H, br s), 2.77 (2H, t, J=6Hz), 3.48 (1H, m), 3.36 (3H, s), 3.07-2.87 (3H, m), 2.75 (1H, dd, J=16, 5Hz), 1.86-1.53 (7H, m), 1.38-1.02 (8H, m), 0.83 (2H, m)

Preparation 52 :

tert-Butyl (3R)-6-cyclohexyl-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}hexanoate



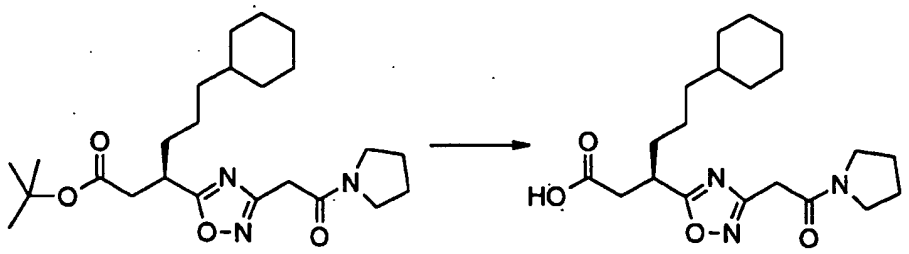
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.70mmol) in dichloromethane (30ml) was treated with 1,1'-carbonyldiimidazole (272mg, 1.70mmol) and the solution was stirred at room temperature for 1 hour. N'-hydroxy-3-oxo-3-(1-pyrrolidinyl)propanimidamide (Patent FR 73-36858 731016) (291mg, 1.70mmol) was then added and the mixture was stirred for 17 hours. The solvent was removed under reduced pressure and the residue was heated neat at 110°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1) to afford the title compound as a colourless oil (309mg).

MS : 434 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.76 (2H, s), 3.56-3.39 (5H, m), 2.80 (1H, dd, J=15, 8Hz), 2.61 (1H, dd, J=15, 4Hz), 1.97 (2H, m), 1.86 (2H, m), 1.81-1.58 (7H, m), 1.41-1.05 (17H, m), 0.83 (2H, m)

Preparation 53:

(3R)-6-Cyclohexyl-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



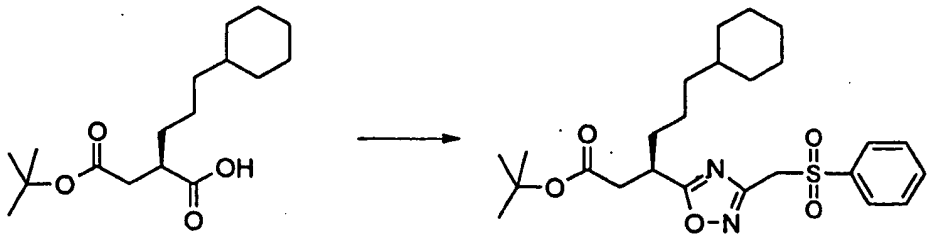
tert-Butyl (3R)-6-cyclohexyl-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 52) (309mg, 0.71mmol) was treated with trifluoroacetic acid (2ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound as a pale yellow oil (200mg).

MS : 378 (MH^+), 400 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 3.83 (2H, s), 3.64-3.40 (5H, m), 2.93 (1H, dd, J=17, 8Hz), 2.76 (1H, dd, J=17, 5Hz), 2.11-1.50 (11H, m), 1.43-1.02 (8H, m), 0.84 (2H, m)

Preparation 54:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(phenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoate



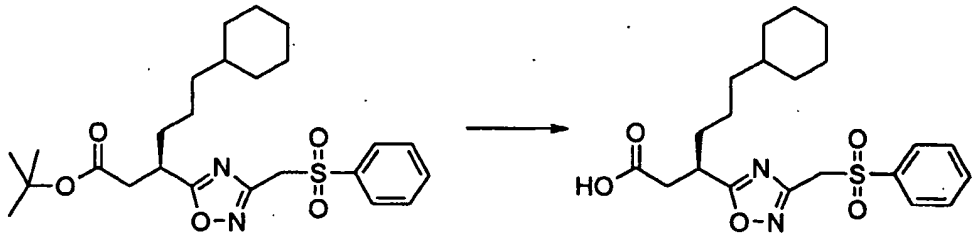
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (300mg, 1.00mmol) in dichloromethane (15ml) was treated with 1,1'-carbonyldiimidazole (162mg, 1.00mmol) and the solution was stirred at room temperature for 2 hours. N'-hydroxy-2-(phenylsulfonyl)ethanimidamide (J.Heterocycl.Chem.; 16; 1979; 1197-1200) (214mg, 1.00mmol) was then added and the mixture was stirred for 17 hours. The solvent was removed under reduced pressure and the residue was heated neat at 130°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1) to afford the title compound (78mg).

MS : 499 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 7.83 (2H, d, J=7Hz), 7.69 (1H, dd, J=7,7Hz), 7.54 (2H, dd, J=7,7Hz), 4.52 (2H, s), 3.43 (1H, m), 2.78 (1H, dd, J=16, 9Hz), 2.60 (1H, dd, J=16, 5Hz), 1.78-1.58 (7H, m), 1.40 (9H, s), 1.30-1.06 (8H, m), 0.85 (2H, m)

Preparation 55:

(3R)-6-Cyclohexyl-3-{3-[(phenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



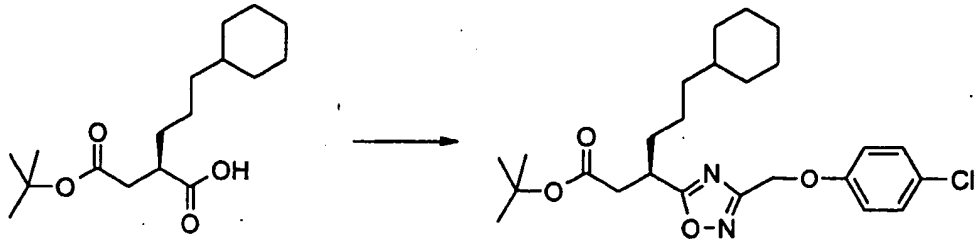
tert-Butyl (3R)-6-cyclohexyl-3-{3-[(phenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 54) (78mg, 0.16mmol) was treated with trifluoroacetic acid (2ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound as an oil which crystallised on standing (60mg).

MS : 421 (MH^+), 438 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, d, J=7Hz), 7.66 (1H, dd, J=7, 7Hz), 7.53 (2H, dd, J=7, 7Hz), 4.53 (2H, s), 3.45 (1H, m), 2.91 (1H, dd, J=16, 9Hz), 2.73 (1H, dd, J=5Hz), 1.80-1.52 (7H, m), 1.39-1.01 (8H, m), 0.84 (2H, m)

Preparation 56:

tert-Butyl (3R)-3-{3-[(4-chlorophenoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate

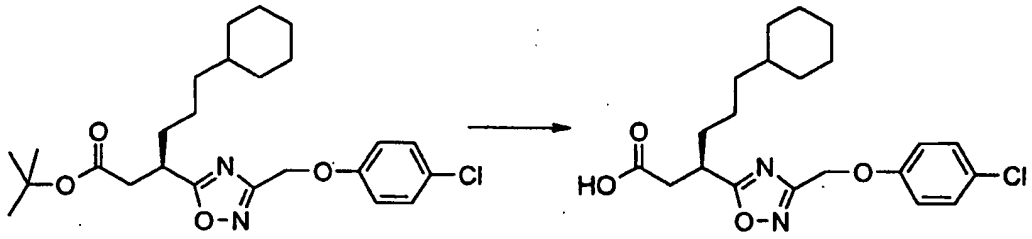


A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (300mg, 1.00mmol) in dichloromethane (15ml) was treated with 1,1'-carbonyldiimidazole (162mg, 1.00mmol) and the solution was stirred at room temperature for 2 hours. 2-(4-chlorophenoxy)-N'-hydroxyethanimidamide (Patent US 97-815671 970313) (197mg, 0.98mmol) was then added and the mixture was stirred for 17 hours. The solvent was removed under reduced pressure and the residue was heated neat at 120°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1) to afford the title compound as a colourless oil (220mg).

^{1}H-NMR ($CDCl_3$) δ : 7.25 (2H, d, J=8Hz), 6.93 (2H, d, J=8Hz), 5.13 (2H, s), 3.48 (1H, m), 2.82 (1H, dd, J=17, 9Hz), 2.64 (1H, dd, J=17, 4Hz), 1.81-1.57 (7H, m), 1.36 (9H, s), 1.33-1.03 (8H, m), 0.83 (2H, m)

Preparation 57:

(3R)-3-{3-[(4-Chlorophenoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid

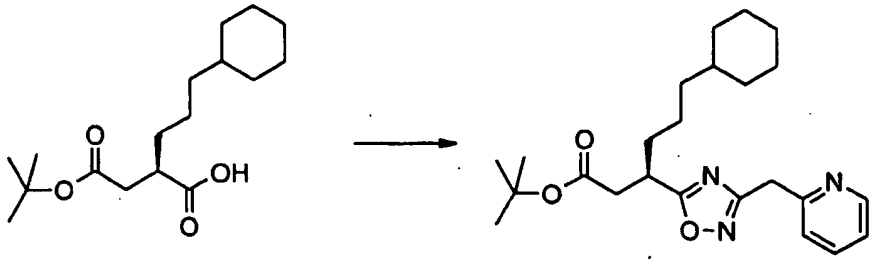


tert-Butyl (3R)-3-{3-[(4-chlorophenoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate (Preparation 56) (215mg, 0.46mmol) was treated with trifluoroacetic acid (5ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene to afford the title compound (189mg).

^{1}H-NMR ($CDCl_3$) δ : 7.25 (2H, d, J=9Hz), 6.94 (2H, d, J=9Hz), 5.14 (2H, s), 3.53 (1H, m), 2.99 (1H, dd, J=15, 9Hz), 2.78 (1H, dd, J=15, 4Hz), 1.85-1.56 (7H, m), 1.35-1.04 (8H, m), 0.84 (2H, m)

Preparation 58:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate



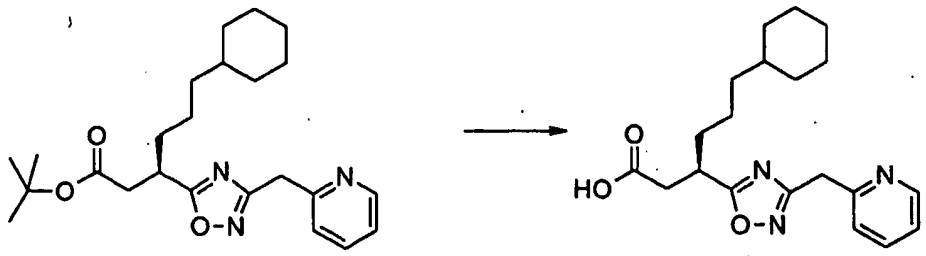
A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (300mg, 1.00mmol) in dichloromethane (15ml) was treated sequentially with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192mg, 1.00mmol), 4-(dimethylamino)pyridine (125mg, 1.02mmol) and N-hydroxy-2-(2-pyridinyl)ethanimidamide (Chem.Pharm.Bull.; 21; 10; 1973; 2146-2160) (152mg, 1.00mmol). The resulting mixture was stirred at room temperature for 17 hours. The solvent was removed under reduced pressure and the residue was heated neat at 120°C under a nitrogen atmosphere for 2 hours. The crude product was then purified by column chromatography on silica gel eluting with dichloromethane : methanol (99 : 1). The residue was further purified by column chromatography on silica gel eluting with ethyl acetate : pentane (30 : 70) to afford the title compound as an oil (107mg).

MS : 414 (MNa^+), 436 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.55 (1H, d, J=5Hz), 7.62 (1H, dd, J= 7, 7Hz), 7.32-7.10 (2H, m), 4.27 (2H, s), 3.45 (1H, m), 2.79 (1H, dd, J=16, 8Hz), 2.60 (1H, dd, J=16, 5Hz), 1.83-1.51 (7H, m), 1.41-1.00 (17H, m), 0.82 (2H, m)

Preparation 59:

(3R)-6-Cyclohexyl-3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid trifluoroacetate



tert-Butyl (3R)-6-cyclohexyl-3-[3-(2-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 58) (247mg, 0.60mmol) was treated with trifluoroacetic acid (7ml) and the resulting mixture was

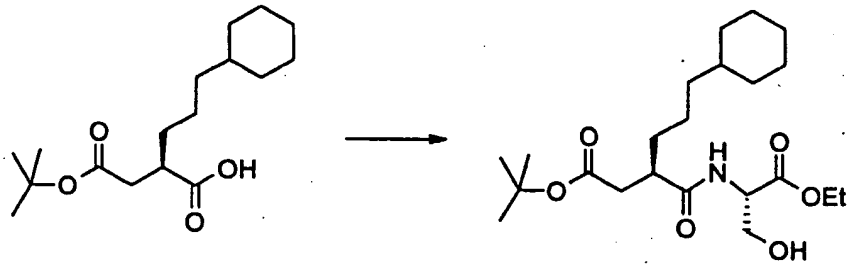
stirred at room temperature under a nitrogen atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene then dichloromethane to afford the title compound as an oil (262mg).

MS : 358 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.75 (1H, d, J=5Hz), 8.04 (1H, dd, J= 7, 7Hz), 7.55 (2H, m), 4.48 (2H, s), 3.49 (1H, m), 2.99-2.61 (2H, m), 1.84-1.44 (7H, m), 1.42-1.00 (8H, m), 0.84 (2H, m)

Preparation 60:

tert-Butyl (3R)-6-cyclohexyl-3-({[(1S)-2-ethoxy-1-(hydroxymethyl)-2-oxoethyl]amino}carbonyl)hexanoate



A solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (5.00g, 16.76mmol) in dichloromethane (75ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (2.49g, 18.43mmol), serine ethyl ester hydrochloride (3.13g, 18.43mmol) and N,N-diisopropylethylamine (6.13ml, 35.19mmol) and the resulting mixture was stirred at 0°C under a nitrogen atmosphere for 15 minutes. 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.53g, 18.43mmol) was then added and the mixture was stirred for 48 hours being allowed to warm to room temperature over this time. The mixture was diluted with dichloromethane (200ml), washed sequentially with water, aqueous citric acid solution (10% w/v), a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was then purified by column chromatography on silica gel eluting a gradient system of ethyl acetate : pentane (10 : 90) to (50 : 50) to afford the title compound as a colourless oil (5.41g).

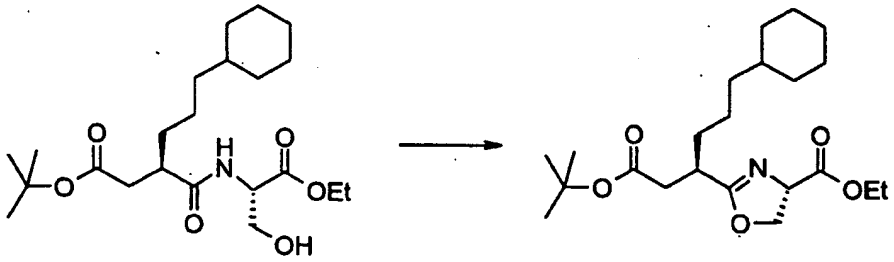
MS : 413 (M^+)

Analysis : Found C, 63.20; H, 9.52; N, 3.27%; $C_{22}H_{39}NO_6$. 0.33 EtOAc requires C, 63.28; H, 9.48; N, 3.16%

^{1}H-NMR ($CDCl_3$) δ : 6.50 (1H, br d, J=6Hz), 4.60 (1H, m), 4.26 (2H, q, J=8Hz), 4.09 (1H, m), 3.85 (1H, m), 3.18 (1H, m), 2.70 (1H, dd, J=18, 9Hz), 2.51 (1H, m), 2.37 (1H, dd, J=18, 3Hz), 1.78-1.52 (7H, m), 1.50-1.02 (20H, m), 0.85 (2H, m)

Preparation 61:

Ethyl (4S)-2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-4,5-dihydro-1,3-oxazole-4-carboxylate

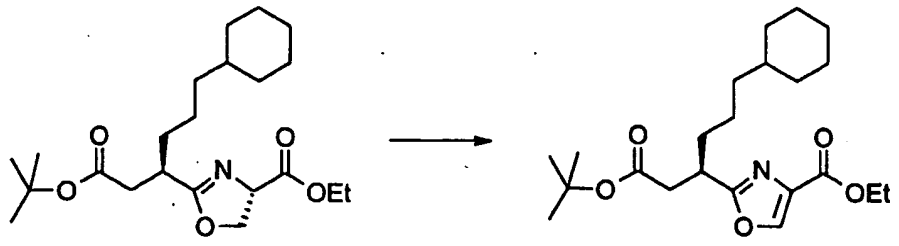


A solution of tert-butyl (3R)-6-cyclohexyl-3-({[(1S)-2-ethoxy-1-(hydroxymethyl)-2-oxoethyl]amino}carbonyl)hexanoate (Preparation 60) (4.14g, 10mmol) in anhydrous tetrahydrofuran (40ml) was treated with (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt [Burgess Reagent] (2.62g, 11mmol) and the resulting mixture was heated under reflux under a nitrogen atmosphere for 1 hour. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (80 : 20) to (50 : 50) to afford the title compound as a colourless oil (3.10g)

^{1}H-NMR ($CDCl_3$) δ : 4.69 (1H, m), 4.52-4.33 (2H, m), 4.22 (2H, m), 2.87 (1H, m), 2.63 (1H, dd, J=16, 7Hz), 2.40 (1H, dd, J=16, 6Hz), 1.76-1.03 (27H, m), 0.85 (2H, m)

Preparation 62:

Ethyl 2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,3-oxazole-4-carboxylate



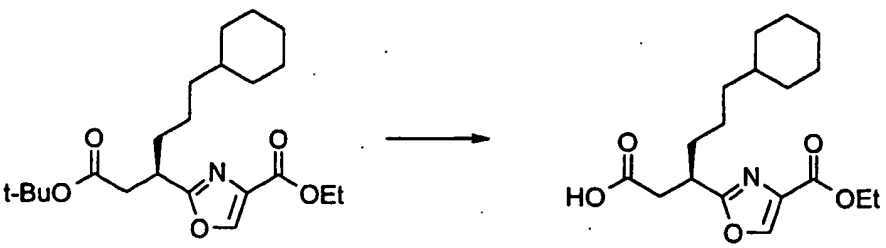
A suspension of copper (II) bromide (2.08g, 9.31mmol) and hexamethylenetetramine (1.30g, 9.31mmol) in degassed dichloromethane (25ml) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (1.39ml, 9.31mmol) and then cooled in a cold water bath and stirred for 5 minutes. This suspension was then treated dropwise with a solution of ethyl (4S)-2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-4,5-dihydro-1,3-oxazole-4-carboxylate (Preparation 61) (0.92g, 2.33mmol) in dichloromethane (5ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and a solution of 0.88 ammonia : saturated aqueous solution of ammonium chloride (1 : 1, 100mls). The layers were separated and the aqueous layer was extracted with ethyl acetate (x2). The organic layers were combined, washed sequentially with hydrochloric acid (2M), saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate : pentane (10 : 90) to afford the title compound as a pale yellow oil (0.59g).

MS : 394 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.13 (1H, s), 4.39 (2H, q, J=7Hz), 3.39 (1H, m), 2.80 (1H, dd, J=17, 8Hz), 2.58 (1H, dd, J=17, 6Hz), 1.84-1.53 (7H, m), 1.49-1.02 (20H, m), 0.84 (2H, m)

Preparation 63:

(3R)-6-Cyclohexyl-3-[4-(ethoxycarbonyl)-1,3-oxazol-2-yl]hexanoic acid trifluoroacetate



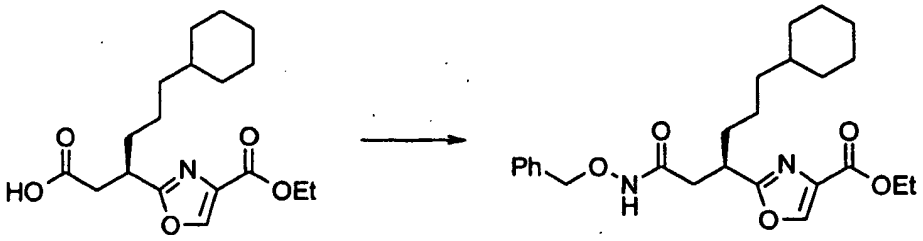
A solution of ethyl 2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,3-oxazole-4-carboxylate (Preparation 62) (1.58g, 4.01mmol) in anhydrous dichloromethane (25ml) was treated with trifluoroacetic acid (7ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane to afford the title compound (1.66g).

MS : 338 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 9.62 (1H, br s), 8.12 (1H, s), 4.34 (2H, q, J=7Hz), 3.39 (1H, m), 2.93 (1H, dd, J=17, 8Hz), 2.67 (1H, dd, J=17, 5Hz), 1.84-1.47 (7H, m), 1.34 (3H, t, J=7Hz), 1.29-0.98 (8H, m), 0.80 (2H, m)

Preparation 64:

Ethyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-1,3-oxazole-4-carboxylate



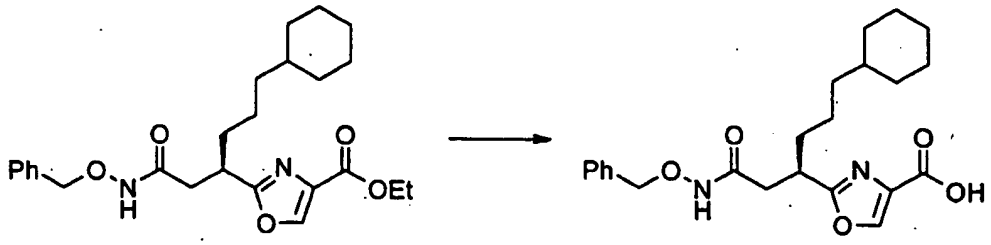
A mixture of (3R)-6-cyclohexyl-3-[4-(ethoxycarbonyl)-1,3-oxazol-2-yl]hexanoic acid trifluoroacetate (Preparation 63) (1.66g, 3.68mmol), 1,1'-carbonyldiimidazole (0.80g, 4.93mmol), O-benzylhydroxylamine hydrochloride (1.57g, 9.84mmol) and N,N-diisopropylethylamine (1.71ml, 9.82mmol) in anhydrous tetrahydrofuran (10ml) was stirred at room temperature for 72 hours. The mixture was diluted with ethyl acetate (50ml) and washed sequentially with a saturated solution of sodium hydrogen carbonate, aqueous citric acid solution (10% w/v) and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol (98 : 2) then further purified by column chromatography on silica gel eluting with ethyl acetate : pentane (50 : 50) to afford the title compound as an orange oil (1.41g)

MS : 443 (MH^+), 465 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.07 (1H, s), 7.40-7.22 (5H, m), 4.85 (2H, s), 4.36 (2H, q, J=7Hz), 3.45 (1H, m), 2.89-2.40 (2H, m), 1.82-1.56 (7H, m), 1.36 (3H, t, J=7Hz), 1.32-1.05 (8H, m), 0.84 (2H, m)

Preparation 65:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-1,3-oxazole-4-carboxylic acid



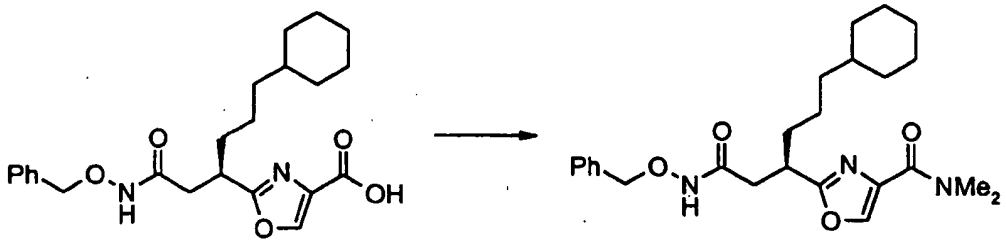
A solution of ethyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-1,3-oxazole-4-carboxylate (Preparation 64) (1.31g, 2.96mmol) in 1,4-dioxane : water (10ml : 5ml) was treated with lithium hydroxide monohydrate (0.19g, 4.44mmol) and stirred in a cold water bath for 3.5 hours. The mixture was diluted with water (100ml) and washed with ethyl acetate. The layers were separated and the aqueous layer was acidified with solid citric acid then extracted with ethyl acetate. The layers were separated and the organic layer was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a white solid (0.75g).

MS : 415 (MH^+), 437 (MNa^+)

^{1}H-NMR (DMSO-d_6) δ : 12.87 (1H, br s), 11.03 (1H, br s), 8.58 (1H, s), 7.41-7.20 (5H, m), 4.70 (2H, s), 3.26 (1H, m), 2.50-2.26 (2H, m), 1.67-1.45 (7H, m), 1.22-0.99 (8H, m), 0.79 (2H, m)

Preparation 66:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N,N-dimethyl-1,3-oxazole-4-carboxamide



A solution of 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-1,3-oxazole-4-carboxylic acid (Preparation 65) (200mg, 0.48mmol) in dichloromethane (6ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (72mg, 0.53mmol), dimethylamine hydrochloride (79mg, 0.96mmol), N-methylmorpholine (160µl, 1.45mmol) and 1-[3-

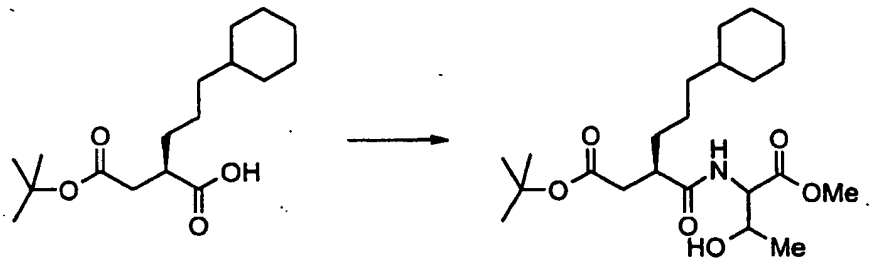
(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (111mg, 0.58mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed sequentially with aqueous citric acid solution (10%w/v), a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was then purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as a colourless oil (200mg).

MS : 442 (MH^+), 464 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 7.99 (1H, s), 7.43-7.20 (5H, m), 4.85 (2H, s), 3.44 (1H, m), 3.39-2.91 (6H, br m), 2.80-2.32 (2H, m), 1.80-1.51 (7H, m), 1.37-1.04 (8H, m), 0.84 (2H, m)

Preparation 67:

tert-Butyl (3R)-6-cyclohexyl-3-({[2-hydroxy-1-(methoxycarbonyl)propyl]amino}carbonyl) hexanoate



An ice-cooled solution of (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (6.40g, 21.45mmol) in dichloromethane (75ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (3.19g, 23.60mmol), threonine methyl ester hydrochloride (4.00g, 23.60mmol), N,N-diisopropylethylamine (7.85ml, 45.10mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.52g, 23.58mmol) and the mixture was stirred for 17 hours being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate then washed sequentially with water, aqueous citric acid solution (10% w/v), a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (100ml) and treated with

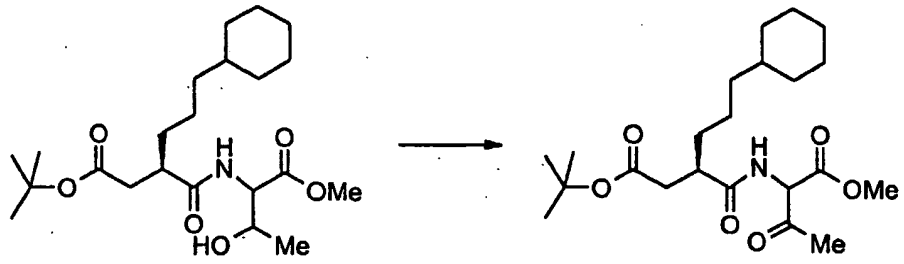
pentane (150ml) to produce a white precipitate. This was filtered off and washed with pentane to afford the title compound as a white powder (6.48g).

MS : 436 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 6.35 (1H, br d), 4.63 (1H, m), 4.26 (1H, m), 3.76 (3H, s), 2.73-2.53 (2H, m), 2.34 (1H, m), 1.73-1.56 (7H, m), 1.45-1.09 (20H, m), 0.84 (2H, m)

Preparation 68:

tert-Butyl (3R)-6-cyclohexyl-3-({[1-(methoxycarbonyl)-2-oxopropyl]amino}carbonyl) hexanoate



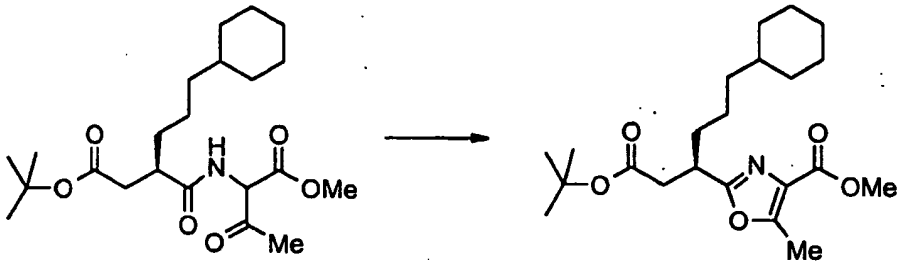
A solution of tert-butyl (3R)-6-cyclohexyl-3-({[2-hydroxy-1-(methoxycarbonyl)propyl]amino}carbonyl) hexanoate (Preparation 67) (6.48g, 15.69mmol) in dichloromethane (60ml) was treated with Dess-Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one] (7.32g, 17.26mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour. A solution of sodium thiosulphate (6g in 50ml water) and a saturated aqueous sodium hydrogen carbonate solution (50ml) were then added to the mixture which was stirred for a further 10 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were sequentially washed with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (100:0 to 90:10) to afford the title compound as a colourless oil (4.86g)

MS : 412 (MH^+), 434 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 6.82 (1H, br d), 5.21 (1H, m), 3.78 (3H, s), 2.72-2.52 (2H, m), 2.40-2.25 (4H, m), 1.72-1.53 (7H, m), 1.45-1.04 (17H, m), 0.83 (2H, m)

Preparation 69:

Methyl 2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-5-methyl-1,3-oxazole-4-carboxylate



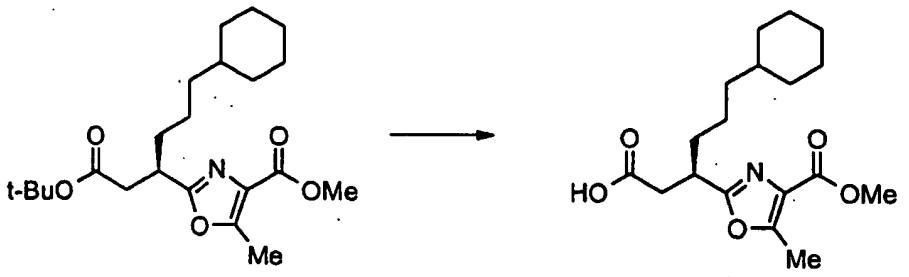
A suspension of triphenylphosphine (9.49g, 36.18mmol), iodine (7.98g, 31.44mmol) and triethylamine (8.49ml, 60.75mmol) in tetrahydrofuran was cooled to -78°C then treated with tert-butyl (3R)-6-cyclohexyl-3-({[1-(methoxycarbonyl)-2-oxopropyl]amino}carbonyl) hexanoate (Preparation 68) (4.86g, 11.80mmol) over 15 minutes. The mixture was stirred at -78°C for 30 minutes then at 0-5°C for 2 hours. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (0: 100 to 10:90) to afford the title compound as a colourless oil (2.92g).

MS : 394 (MH^+), 416 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 3.89 (3H, s), 3.29 (1H, m), 2.74 (1H, dd, J=14, 6Hz), 2.60-2.49 (4H, m), 1.79-1.54 (7H, m), 1.38 (9H, s), 1.31-1.05 (8H, m), 0.82 (2H, m)

Preparation 70:

(3R)-6-Cyclohexyl-3-[4-(methoxycarbonyl)-5-methyl-1,3-oxazol-2-yl]hexanoic acid



A solution of methyl 2-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-5-methyl-1,3-oxazole-4-carboxylate (Preparation 69) (2.92g, 7.43mmol) in anhydrous dichloromethane (15ml) was treated with trifluoroacetic acid (7.5ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 24 hours. The solvent was removed under reduced pressure and the residue was azeotroped with dichloromethane (x3). The residue was purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate : pentane (0:100 to 40:60) to afford the title compound as a colourless oil (2.50g).

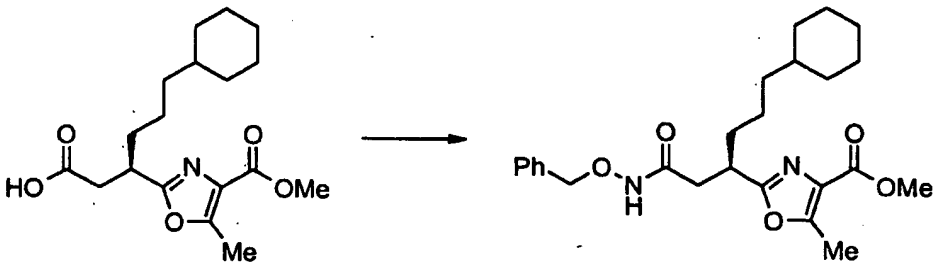
MS : 338 (MH^+), 360 (MNa^+)

Analysis : Found C, 62.90; H, 8.18; N, 3.93%; $C_{18}H_{27}NO_5$. 0.3 EtOAc requires C, 63.38;H, 8.14; N, 3.85%

^{1}H-NMR ($CDCl_3$) δ : 3.86 (3H, s), 3.33 (1H, m), 2.92 (1H, dd, J=17, 8Hz), 2.67 (1H, dd, J=17, 5Hz), 2.58 (3H, s), 1.81-1.56 (7H, m), 1.34-1.03 (8H, m), 0.81 (2H, m)

Preparation 71:

Methyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylate



A solution of (3R)-6-cyclohexyl-3-[4-(methoxycarbonyl)-5-methyl-1,3-oxazol-2-yl]hexanoic acid (Preparation 70) (2.48g, 7.36mmol) was cooled to 0° and treated with 1-hydroxybenzotriazole hydrate (994mg, 7.36mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.12g, 11.06mmol) and N-methylmorpholine (1.21ml, 11.04mmol). The mixture was stirred for 15 minutes then treated with O-benzylhydroxyamine (1.17g, 7.36mmol) and further N-methylmorpholine (0.81ml, 7.36mmol). The mixture was stirred for 1 hour being allowed to warm to room temperature over this time. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed sequentially with water, a saturated solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and

the solvent removed under reduced pressure to afford the title compound as a colourless oil (3.22g)

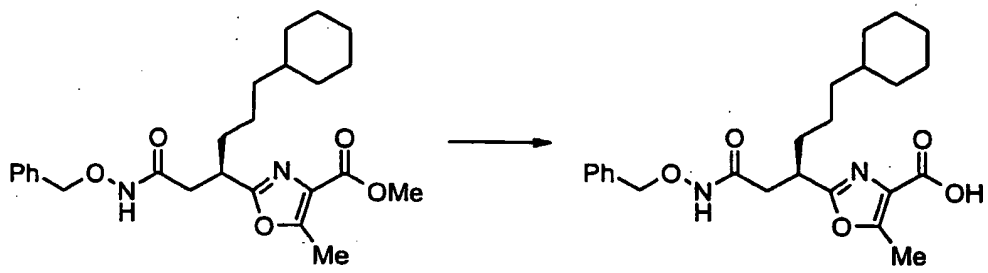
MS : 443 (MH^+), 465 (MNa^+)

Analysis : Found C, 66.78; H, 7.77; N, 6.19%; $C_{25}H_{34}N_2O_5$. 0.3 EtOAc requires C, 67.10;H, 7.82; N, 5.97%

^{1}H-NMR ($CDCl_3$) δ : 8.62 (1H, br s), 7.33 (5H, m), 4.84 (2H, s), 3.84 (3H, s), 3.36 (1H, m), 2.70-2.33 (5H, m), 1.78-1.54 (7H, m), 1.30-1.03 (8H, m), 0.82 (2H, m)

Preparation 72:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylic acid



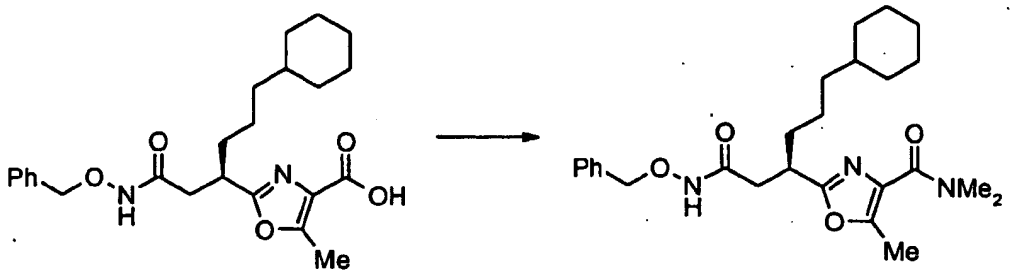
A solution of methyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylate (Preparation 71) (1.00g, 2.26mmol) in 1,4-dioxane (10ml) was treated with an aqueous sodium hydroxide solution (1N, 1.5ml) and stirred at room temperature for 4 hours. Further aqueous sodium hydroxide (1N, 3.0ml) was added and the mixture was stirred for 20 hours. The solvent was removed under reduced pressure and the residue was dissolved in water and washed with ethyl acetate. The layers were separated and the aqueous layer was acidified with solid citric acid then extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a white foam (0.83g).

MS : 427 (MH^-)

^{1}H-NMR ($CDCl_3$) δ : 7.34 (5H, m), 4.85 (2H, s), 3.40 (1H, m), 2.71-2.33 (5H, m), 1.76-1.51 (7H, m), 1.32-1.03 (8H, m), 0.83 (2H, m)

Preparation 73:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N,N,5-trimethyl-1,3-oxazole-4-carboxamide



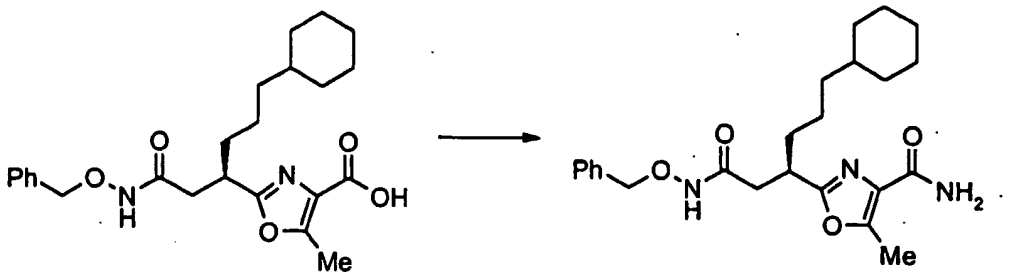
A solution of methyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylate (Preparation 72) (152mg, 0.36mmol) in dichloromethane (5ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (48mg, 0.36mmol), N-methylmorpholine (82µl, 0.75mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (75mg, 0.39mmol) and dimethylamine hydrochloride (29mg, 0.36mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 17 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed sequentially with water, a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95 : 5 : 0.5) to afford the title compound as a colourless oil which crystallised on standing (109mg).

MS : 456 (MH^+), 478 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.53 (1H, br s), 7.34 (5H, m), 4.84 (2H, s), 3.36 (1H, m), 3.27-2.86 (6H, br m), 2.64-2.31 (5H, m), 1.74-1.50 (7H, m), 1.31-1.03 (8H, m), 0.82 (2H, m)

Preparation 74:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxamide



A solution of methyl 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylate (Preparation 72) (200mg, 0.47mmol) in dichloromethane (10ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (63mg, 0.47mmol), N-methylmorpholine (77µl, 0.70mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (134mg, 0.70mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 10 minutes. Concentrated ammonia solution (0.88, 50µl, 1.00mmol) was then added and the mixture was stirred for 17 hours. The mixture was diluted with dichloromethane and washed sequentially with water, a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was then purified by column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (97 : 3 : 0.3) to afford the title compound as a white solid (140mg).

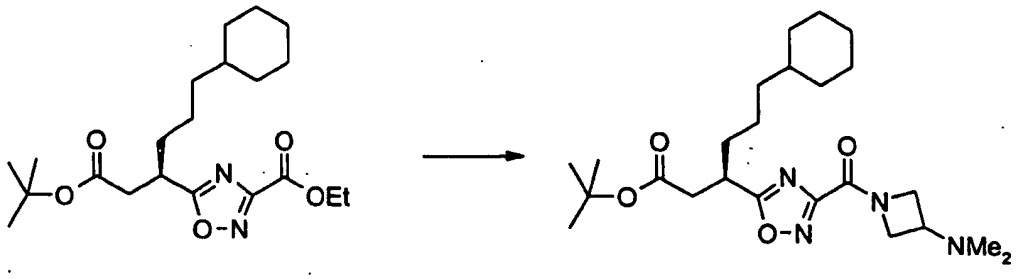
MS : 426(MH^+)

Analysis : Found C, 67.45; H, 7.85; N, 9.64%; $C_{24}H_{33}N_3O_4$ requires C, 67.42;H, 7.78; N, 9.83%

^{1}H-NMR ($CDCl_3$) δ : 7.36 (5H, m), 4.86 (2H, s), 3.36 (1H, m), 2.72-2.37 (5H, m), 1.75-1.53 (7H, m), 1.42-1.05 (8H, m), 0.84 (2H, m).

Preparation 75:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[3-(dimethylamino)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



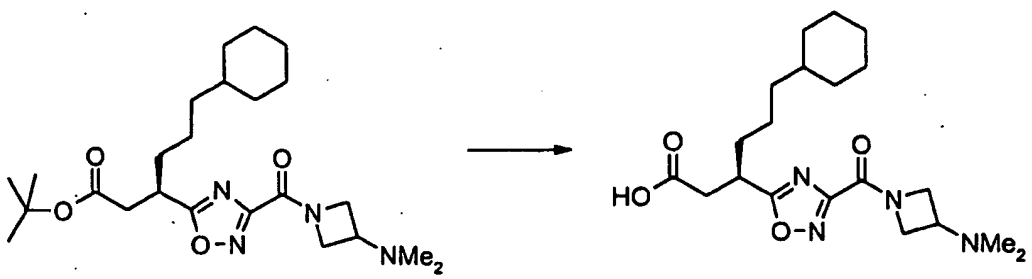
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (360mg, 0.91mmol) and triethylamine (370mg, 3.65mmol) in ethanol (5ml) was treated with N,N-dimethyl-3-azetidinamine (J.Med.Chem.;36; 801; 1993) (300mg, 0.91mmol) and the resulting mixture was heated at 80°C under a nitrogen atmosphere for 16 hours. The mixture was partitioned between ethyl acetate (150ml) and saturated aqueous ammonium chloride solution (150ml). The organic layer was washed with saturated ammonium chloride solution (150ml), water (150ml) and brine (150ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate : diethylamine (87.5 : 12.5 : 0.25) gradually changing to pentane : ethyl acetate : diethylamine (50 : 50 : 1) to afford the title compound as a colourless oil (355mg).

MS: 449(MH^+), 471(MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.56 (1H, dd), 4.38 (1H, dd), 4.21 (1H, dd), 4.05 (1H,dd), 3.50 (1H, m), 3.17 (1H, m), 2.86 (1H, dd), 2.63 (1H, dd), 2.19 (6H, s), 1.78 (1H, m), 1.65 (6H, br t), 1.39 (9H, s), 1.08-1.28 (8H, m), 0.82 (2H, m).

Preparation 76:

(3R)-6-Cyclohexyl-3-(3-{[3-(dimethylamino)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



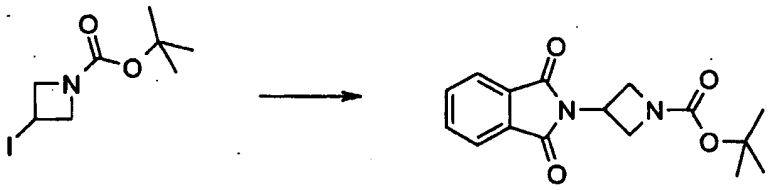
A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[3-(dimethylamino)-1-azetidinyl]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 75) (340mg, 0.76mmol) in trifluoroacetic acid (10ml) was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane. The residue was dissolved in ethyl acetate (50ml) and washed with saturated aqueous ammonium chloride solution (50ml) and brine (50ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a white solid (30mg). The combined aqueous washes were extracted with dichloromethane, containing <10% methanol, (3 x 150ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a white solid (180mg), combined total mass 210mg.

MS : 393 (MH^+), 415 (MNa^+)

^{1}H-NMR (CD_3OD) δ : 4.88 (1H, m), 4.70 (1H, m), 4.49 (1H, dd), 4.31 (1H, dd), 4.13 (1H, m), 3.05 (1H, m), 2.91 (1H, dd), 2.35 (6H, s), 2.79 (1H, dd), 1.78 (2H, q), 1.58-1.73 (5H, m), 1.09-1.3.5 (8H, m), 0.70-0.93 (2H, br q).

Preparation 77:

tert-Butyl 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-azetidinecarboxylate



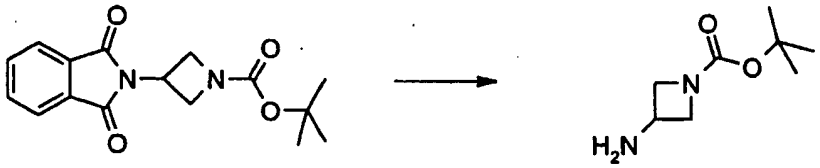
A solution of tert-butyl 3-iodocyclobutanecarboxylate (EP 992493) (5.0g, 17.7mmol) in dimethylformamide was treated with potassium phthalimide (5.0g, 27.0mmol) and heated at 100°C for 18 hours. The reaction mixture was filtered, to remove the excess potassium phthalimide, which was washed with dimethylformamide (10ml). The filtrate was concentrated under reduced pressure and the residue azeotroped with xylene (2x30ml). The residue was purified by column chromatography on silica gel eluting with a gradient system of 95 : 5 (pentane : ethyl acetate) gradually changing to 55 : 45 (pentane : ethyl acetate) to afford the title compound as a white solid (3.78g).

MS : 325 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 7.84 (2H, m), 7.72 (2H, m), 5.01 (1H, m), 4.50 (2H, m), 4.20 (2H, m), 1.40 (9H, s).

Preparation 78:

tert-Butyl 3-amino-1-azetidinecarboxylate



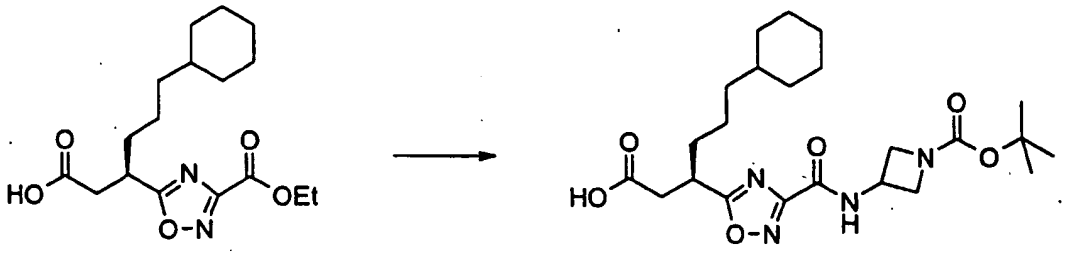
A solution of tert-butyl 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-azetidinecarboxylate (Preparation 77) in methylamine in methanol (2M) (10ml) was stirred in a sealed tube at 55°C for 3 hours. On cooling a precipitate formed and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100ml) and washed with water (100ml, containing (2M) hydrochloric acid (3ml)) and water (50ml, containing (2M) hydrochloric acid (2ml)). The combined aqueous was basified with (2M) sodium hydroxide solution (20ml) and extracted with ethyl acetate (3x75ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of 97.5 : 2.5 : 0.25 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound (935mg) of approximately 90% purity, which was used in preparation without further purification.

MS : 173 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.11 (2H , m), 3.76 (1H, m), 3.57 (2H, m), 1.41 (9H, s).

Preparation 79:

(3R)-3-[3-({[1-(tert-Butoxycarbonyl)-3-azetidinyl]amino}carbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



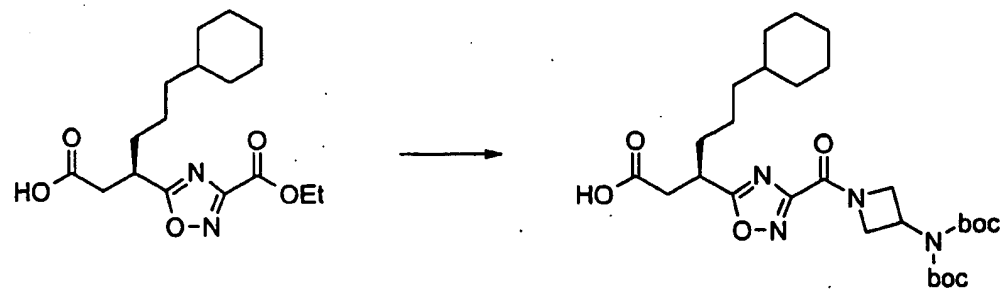
A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (480mg, 1.42mmol) and triethylamine (1ml, 7.18mmol) in ethanol (8ml) was treated with tert-butyl 3-amino-1-azetidinecarboxylate (Preparation 78) (300mg, 1.74mmol) and the resulting mixture was heated at 80°C under a nitrogen atmosphere for 18 hours. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (90 : 10) to afford the title compound contaminated with starting amine. The solid was dissolved in ethyl acetate and washed with hydrochloric acid (0.5M) (2x), water and brine, dried over magnesium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a sticky foam.

MS : 463 $(M-H)^-$

^{1}H-NMR ($CDCl_3$) δ : 7.64 (1H, d), 4.80 (1H, m), 4.25 (2H, t), 3.88 (2H, dd), 3.97 (1H, dd), 2.79 (1H, dd), 1.57-1.80 (8H, m), 1.38 (9H, s), 1.03-1.20 (8H, m), 0.80 (2H, m).

Preparation 80:

(3R)-3-[3-({3-[bis(tert-Butoxycarbonyl)amino]-1-azetidinyl}carbonyl)-1,2,4-oxadiazol-5-yl]-6-cyclohexylhexanoic acid



A solution of (3R)-6-cyclohexyl-3-[3-(ethoxycarbonyl)-1,2,4-oxadiazol-5-yl]hexanoic acid (Preparation 4) (480mg, 1.26mmol) and triethylamine (350 l, 2.50mmol) in ethanol (8ml) was

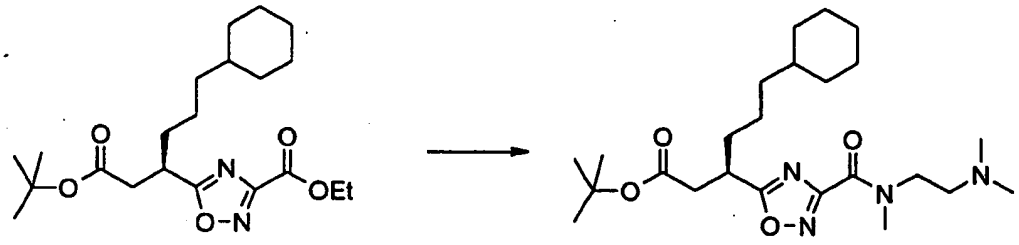
treated with di(tert-butyl) 3-azetidinylimidodicarbonate (EP 153163, EP 106489) (1.00g, 4.56mmol) and the resulting mixture was heated at 80°C under a nitrogen atmosphere for 18 hours. The solvent was removed under reduced pressure. The solid was dissolved in ethyl acetate and washed with water, to which the minimal amount of hydrochloric acid (2M) was added to reach pH 2, hydrochloric acid (0.5M) (2x), water and brine, dried over magnesium sulphate, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane : methanol (99 : 1) gradually changing to dichloromethane : methanol (90 : 10) to afford the title compound (440mg).

MS : 563 $(M-H)^-$

^{1}H-NMR ($CDCl_3$) δ : 4.78 (2H, m), 4.60 (1H, m), 4.45 (1H, t), 4.26 (1H, dd), 2.98 (1H, dd), 2.78 (1H, dd), 1.60-2.0 (7H, m), 1.49 (9H, s), 1.08-1.35 (8H, m), 0.82 (2H, m).

Preparation 81:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



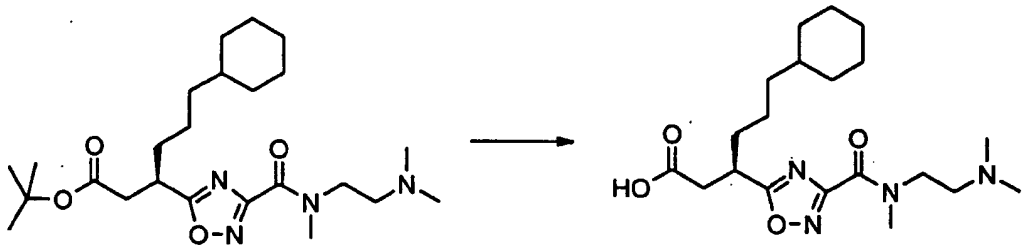
A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (560mg, 1.42mmol) in ethanol (2ml) was treated with N,N,N'-trimethylethylenediamine (900 l, 0.91mmol) and the resulting mixture was heated at 85°C in a sealed tube for 4.5 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with a system of 95 : 5 : 0.5 (dichloromethane : methanol : ammonia) to afford the title compound as a colourless oil (632mg).

MS : 451 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 3.64 (1H, br s), 3.51 (2H, m), 3.14 (3H, s), 2.83 (1H, dd), 2.65 (1H, dd), 2.43-2.60 (2H br d), 2.28 (3H, br s), 2.19 (3H, br s), 1.58-1.85 (7H, m), 1.39 (9H, s), 1.07-1.36 (8H, m), 0.84 (2H, m).

Preparation 82:

(3R)-6-Cyclohexyl-3-(3-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 81) (630mg, 1.40mmol) in dichloromethane (5ml) was treated with trifluoroacetic acid (5ml) and stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane. The residue was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 (dichloromethane : methanol) gradually changing to 90 : 10 (dichloromethane : methanol) to afford the title compound as a colourless gum (453 mg).

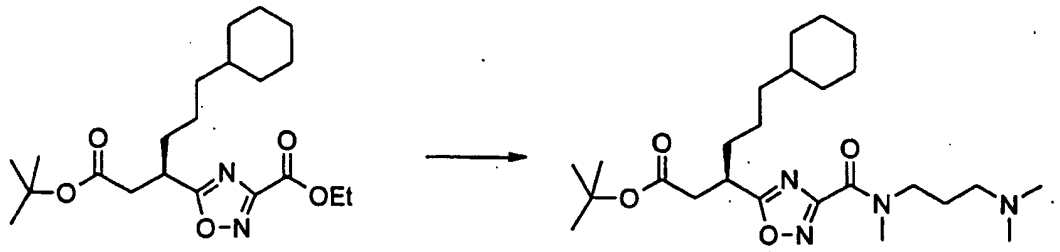
MS : 395 (MH^+)

Analysis : Found, C, 46.50; H, 6.00; N, 9.13%; $C_{20}H_{34}N_4O_4$. 2 CF_3CO_2H requires C, 46.30; H, 5.83; N, 9.00%

^{1}H-NMR ($CDCl_3$) δ : 3.88 (1H, m), 3.76 (1H, m), 3.52 (1H, m), 3.05-3.40 (5H, m), 2.70-3.00 (7H, m), 1.57-1.90 (6H, m), 1.08-1.40 (7H, m), 0.84 (2H, m).

Preparation 83:

tert-Butyl (3R)-6-cyclohexyl-3-(3-{[[3-(dimethylamino)propyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (550mg, 1.40mmol) in ethanol (2ml) was treated with N,N,N'-trimethyl-1,3-propanediamine (1.02ml, 7.00mmol) and the resulting mixture was heated at 85°C in a sealed tube for 3 hours. The solvent removed under reduced pressure. The residue was purified by column chromatography on silica eluting with a gradient system of 97 : 3 : 0.3 (dichloromethane : methanol : ammonia) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : ammonia) to afford the title compound as a colourless oil (512mg).

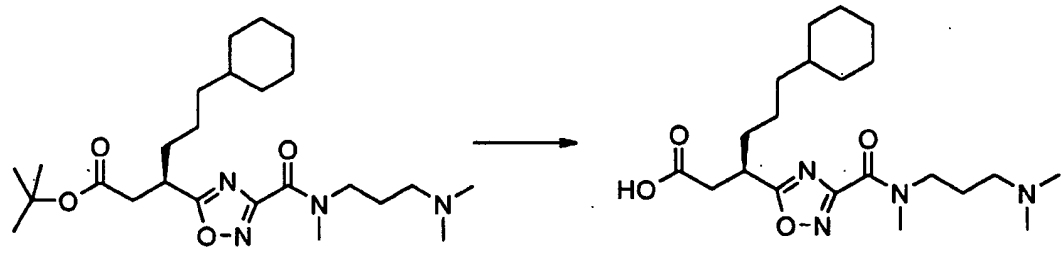
MS : 465 (MH^+)

Analysis : Found, C, 64.44; H, 9.72; N, 12.07%; $C_{25}H_{44}N_4O_4$ requires C, 64.62; H, 9.54; N, 12.06%

^{1}H-NMR ($CDCl_3$) δ : 3.58 (1H, t), 3.50 (1H, t), 3.44 (1H, t), 3.09 (3H, d), 2.83 (1H, m), 2.64 (1H, dd), 2.35 (1H, t), 2.23 (3H, s), 2.20 (1H, m), 2.15 (3H, s), 1.58-1.88 (8H, m), 1.40 (9H, s), 1.06-1.37 (7H, m), 0.84 (2H, m).

Preparation 84:

(3R)-6-Cyclohexyl-3-(3-{[[3-(dimethylamino)propyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-(3-{[[3-(dimethylamino)propyl](methyl)amino]carbonyl}-1,2,4-oxadiazol-5-yl)hexanoate (Preparation 83) (500mg, 1.08mmol) in dichloromethane (5ml) was treated with trifluoroacetic acid (5ml) and stirred at room temperature for 4.5 hours. The solvent was removed under reduced pressure and the residue azeotroped from dichloromethane. The residue was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 (dichloromethane : methanol) gradually changing to 80 : 20 (dichloromethane : methanol) to afford the title compound as a colourless glass (595mg).

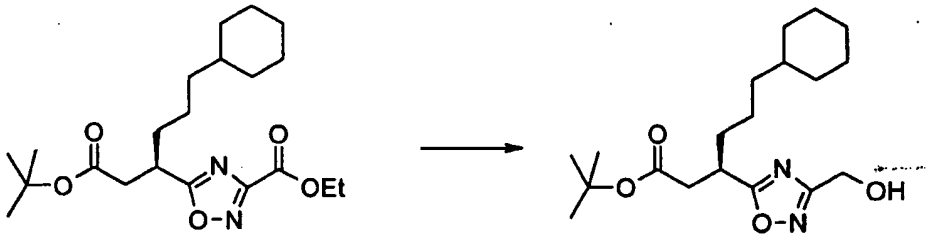
MS : 409 (MH^+)

Analysis : Found, C, 45.48; H, 5.84; N, 8.50%; $C_{21}H_{36}N_4O_4$. 2 CF_3CO_2H. $2H_2O$ requires C, 45.87; H, 6.16; N, 8.56%

^{1}H-NMR ($CDCl_3$) δ : 3.52 (2H, m), 3.37 (1H, m), 3.09 (3H, m), 2.99 (2H, t), 2.81 (6H, s), 1.98 (2H, m), 1.58-1.90 (7H, m), 1.05-1.44 (8H, m), 0.88 (2H, m).

Preparation 85:

tert-Butyl (3R)-6-cyclohexyl-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate



A solution of ethyl 5-{(1R)-1-[2-(tert-butoxy)-2-oxoethyl]-4-cyclohexylbutyl}-1,2,4-oxadiazole-3-carboxylate (Preparation 3) (15.2g, 38.50mmol) in ethanol (120ml) was treated with portions of sodium borohydride (1.46g, 38.50mmol) and the resulting mixture was was stirred at room temperature under a nitrogen atmosphere for 5 hours. Aqueous citric acid (5%$^w/_v$ solution) was added slowly and the mixture was stirred at room temperature for a further 30 minutes. The organic solvent was removed under reduced pressure. The aqueous layer was diluted with water and extracted with ethyl acetate giving an emulsion. Anhydrous sodium chloride was added to break up the emulsion. The combined organic layers were washed with saturated sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulphate, filtered

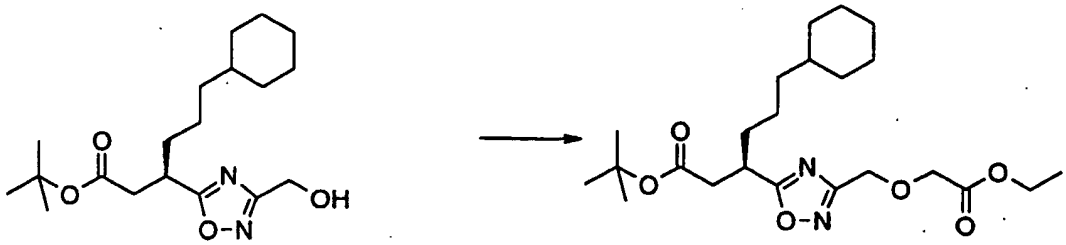
and the solvent removed under reduced pressure to afford the title compound as a colourless oil (13.4g).

MS : 375 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.77 (2H, s), 3.46 (1H, m), 2.80 (1H, dd), 2.62 (1H, dd), 1.58-1.80 (7H, m), 1.39 (9H, s), 1.07-1.33 (8H, m), 0.82 (2H, m).

Preparation 86:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoate



A suspension of sodium hydride 60% suspension in mineral oil (13mg, 0.33mmol) in anhydrous tetrahydrofuran (1ml) was cooled to 0°C and treated with a solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 85) (105mg, 0.30mmol) in anhydrous tetrahydrofuran (1ml) and stirred under a nitrogen atmosphere for 1 hour. Ethyl bromoacetate (37µl, 0.33mmol) was added and the mixture was stirred for 18 hours, being allowed to warm to room temperature over this time. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (99 : 1) to pentane : ethyl acetate (80 : 20) to afford the title compound as a colourless oil (84mg).

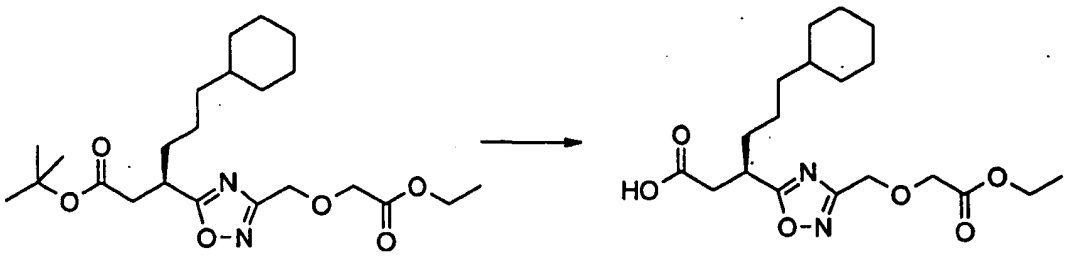
MS : 461 (MNa^+)

Analysis : Found, C, 62.87; H, 8.77; N, 6.39%; $C_{23}H_{38}N_2O_6$ requires C, 62.99; H, 8.73; N, 6.39%

^{1}H-NMR ($CDCl_3$) δ : 4.75 (2H, s), 4.20 (4H, m), 3.45 (1H, m), 2.80 (1H, dd), 2.60 (1H, dd), 1.6-1.8 (7H, m), 1.40 (9H, s), 1.10-1.30 (11H, m), 0.94 (2H, m).

Preparation 87:

(3R)-6-Cyclohexyl-3-{3-[(2-ethoxy-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 86) (500mg, 1.08mmol) in dichloromethane (7ml) was treated with trifluoroacetic acid (3ml) and stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene and dichloromethane. The oil was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 : 0 (dichloromethane : methanol : acetic acid) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : acetic acid) to afford the title compound as a colourless oil (374mg).

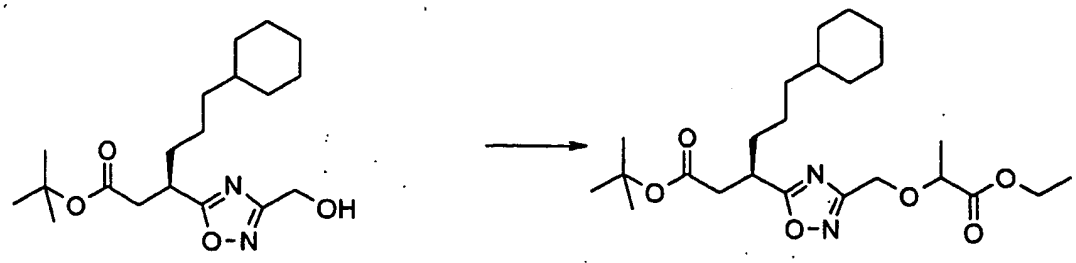
MS : 383 (MH^+)

Analysis : Found, C, 59.67; H, 7.91; N, 7.32%; $C_{19}H_{30}N_2O_6$. 0.05 H_2O. 0.05 CH_2Cl_2 requires C, 59.62; H, 7.90; N, 7.22%

^{1}H-NMR ($CDCl_3$) δ : 4.75 (2H, s), 4.20 (4H, m), 3.51 (1H, m), 2.98 (1H, dd), 2.75 (1H, dd), 1.60-1.80 (7H, m), 1.10-1.30 (11H ,m), 0.82 (2H, m).

Preparation 88:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-1-methyl-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoate



A suspension of sodium hydride 60% suspension in mineral oil (18mg, 0.45mmol) in anhydrous tetrahydrofuran (1ml) was cooled to 0°C and treated with a solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 85) (142mg, 0.40mmol) in anhydrous tetrahydrofuran (1ml) and stirred under a nitrogen atmosphere for 0.5 hours. Ethyl 2-bromopropionate (37µl, 0.33mmol) was added and the mixture was stirred for 2 days, being allowed to warm to room temperature over this time. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (99 : 1) to pentane : ethyl acetate (0 : 100) to afford the title compound as a colourless oil (90mg).

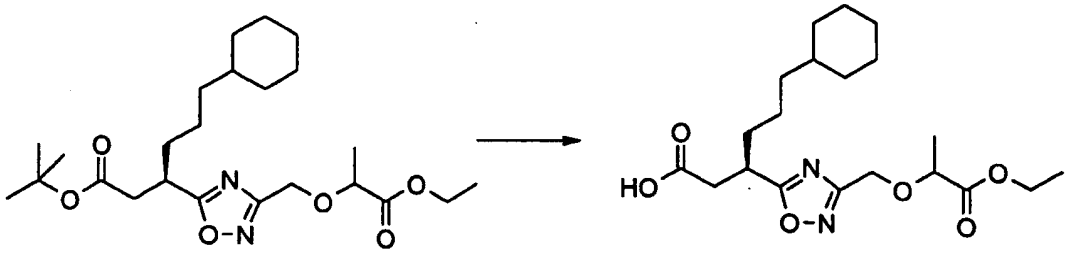
MS : 475 (MNa^+)

Analysis : Found, C, 63.57; H, 8.93; N, 6.19%; $C_{24}H_{40}N_2O_8$ requires C, 63.69; H, 8.91; N, 6.19%

^{1}H-NMR ($CDCl_3$) δ : 4.79 (1H, d), 4.58 (1H, d), 4.20 (3H, m), 3.45 (1H, m), 2.78 (1H, dd), 2.60 (1H, dd), 1.60-1.80 (7H, m), 1.42 (3H, d), 1.35 (9H, s), 1.10-1.30 (11H, m), 0.83 (2H, m).

Preparation 89:

(3R)-6-Cyclohexyl-3-{3-[(2-ethoxy-1-methyl-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(2-ethoxy-1-methyl-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 88) (480mg, 1.06mmol) in dichloromethane (8ml) was treated with trifluoroacetic acid (3.5ml) and stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene and dichloromethane. The oil was purified by column chromatography on silica gel eluting with a

gradient system of 100 : 0 : 0 (dichloromethane : methanol : acetic acid) gradually changing to 95 : 5 : 0.5 (dichloromethane : methanol : acetic acid) to afford the title compound as a colourless oil (395mg).

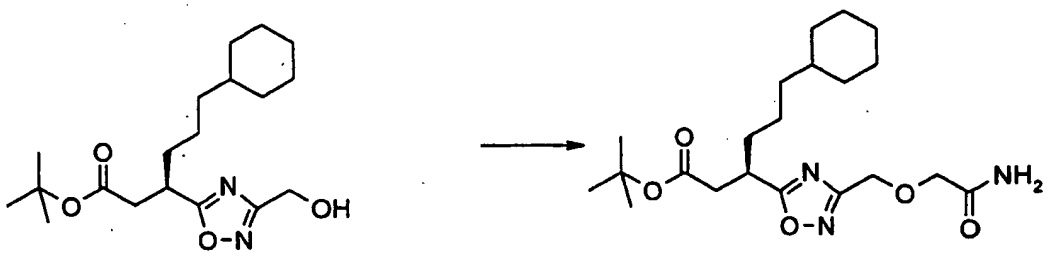
MS : 419 (MNa^+)

Analysis : Found, C, 60.03; H, 8.21; N, 6.97%; $C_{20}H_{32}N_2O_6$. 0.2 CH_2Cl_2 requires C, 60.04; H, 8.16; N, 7.00%

^{1}H-NMR ($CDCl_3$) δ : 4.80 (1H, d), 4.58 (1H, d), 4.10-4.30 (3H, m), 3.50 (1H, m), 2.98 (1H, dd), 2.75 (1H, dd), 1.60-1.80 (7H, m), 1.45 (3H, d), 1.10-1.30 (11H, m), 0.83 (2H, m).

Preparation 90:

tert-Butyl (3R)-3-{3-[(2-amino-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate



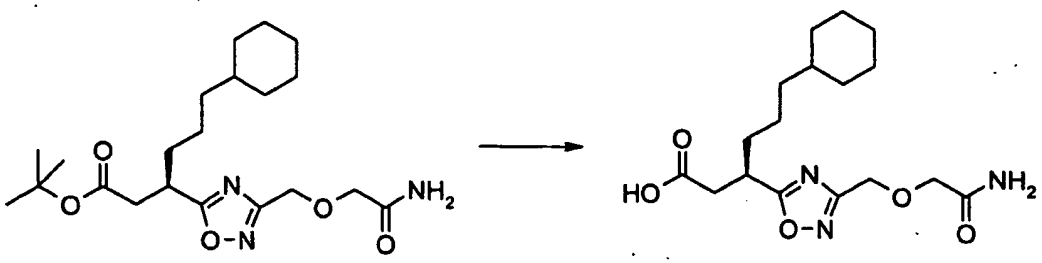
A suspension of sodium hydride 60% suspension in mineral oil (51mg, 1.28mmol) in anhydrous tetrahydrofuran (3ml) was cooled to 0°C and treated with a solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 85) (105mg, 0.30mmol) in anhydrous tetrahydrofuran (3ml) and stirred under a nitrogen atmosphere for 30 minutes. 2-Bromoacetamide (235mg, 1.70mmol) was added and the mixture was allowed to warm to room temperature and then heated at 40°C for 15 hours. The cooled reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The solid was purified by column chromatography on silica gel eluting with a gradient system of pentane : ethyl acetate (99 : 1) to pentane : ethyl acetate (0 : 100) to afford the title compound as a colourless oil (330mg).

MS : 432 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.68 (2H, s), 4.10 (2H, s), 3.46 (1H, m), 2.79 (1H, dd), 2.62 (1H, dd), 1.6-1.8 (7H, m), 1.40 (9H, s), 1.10-1.30 (8H, m), 0.84 (2H, m).

Preparation 91:

(3R)-3-{3-[(2-Amino-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoic acid



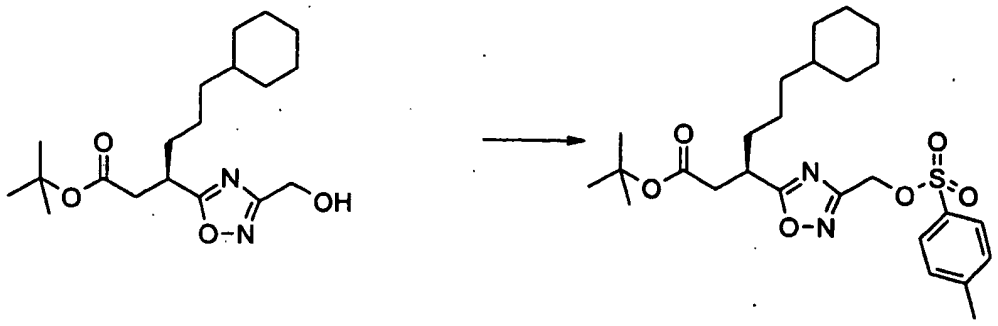
A solution of tert-butyl (3R)-3-{3-[(2-amino-2-oxoethoxy)methyl]-1,2,4-oxadiazol-5-yl}-6-cyclohexylhexanoate (Preparation 90) (280mg, 0.86mmol) in dichloromethane (7ml) was treated with trifluoroacetic acid (3ml) and stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene and dichloromethane. The oil was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 : 0 (dichloromethane : methanol : acetic acid) gradually changing to 90 : 10 : 1 (dichloromethane : methanol : acetic acid) to afford a colourless oil which was triturated with diethyl ether and filtered to afford the title compound (155mg).

MS : 376 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 6.60-6.80 (2H, br d) 4.70 (2H, s), 4.08 (2H, dd), 3.48 (1H, m), 2.85 (1H, dd), 2.73 (1H, dd), 1.60-1.80 (7H, m), 1.10-1.40 (8H ,m), 0.82 (2H, m).

Preparation 92:

tert-Butyl (3R)-6-cyclohexyl-3-[3-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1,2,4-oxadiazol-5-yl]hexanoate



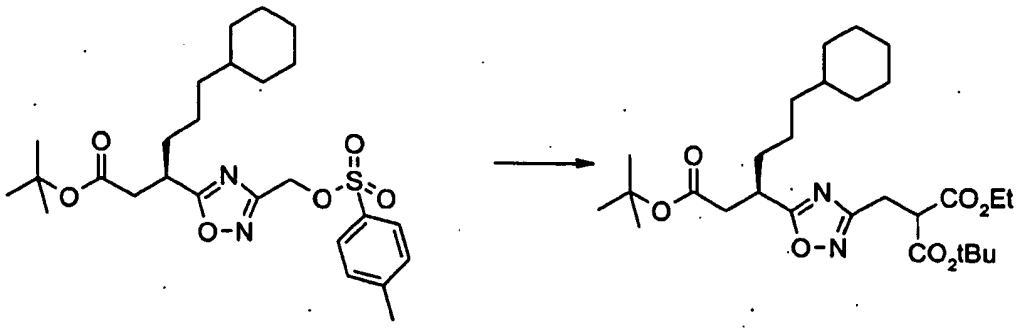
A suspension of sodium hydride 60% suspension in mineral oil (1.52g, 38.00mmol) in anhydrous tetrahydrofuran (30ml) was cooled to 0°C and treated with a solution of tert-butyl (3R)-6-cyclohexyl-3-[3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 85) (13.40g, 38.00mmol) in anhydrous tetrahydrofuran (120ml) and stirred under a nitrogen atmosphere for 30 minutes. p-Toluene sulphonyl chloride (7.25g, 38.00mmol) was added portionwise and the mixture was allowed to warm to room temperature over 18 hours. The solvent was removed under reduced pressure The residue was dissolved in ethyl acetate and washed with water, saturated sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with dichloromethane to afford the title compound (10.75g).

MS : 529 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 7.80 (2H, d), 7.33 (2H, d), 5.12 (2H, s), 3.40 (1H, m), 2.72 (1H, dd), 2.58 (1H, dd), 2.43 (3H, s), 1.56-1.78 (7H, m), 1.35 (9H, s), 1.05-1.30 (8H, m), 0.82 (2H, m).

Preparation 93:

1-tert-Butyl 3-ethyl 2-({5-[(1R)-1-(2-tert-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl}methyl)malonate



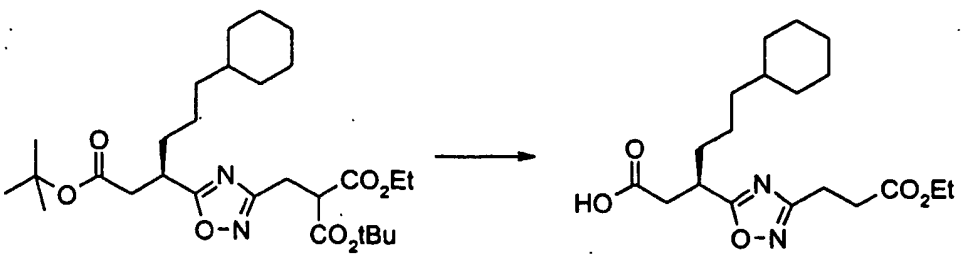
A suspension of sodium hydride 60% suspension in mineral oil (35mg, 38.00mmol) in anhydrous tetrahydrofuran (3ml) was cooled to 0°C and treated with tert-butylethyl malonate (13.40g, 38.00mmol), stirred under a nitrogen atmosphere for 5 minutes and then allowed to warm to room temperature. A solution of tert-butyl (3R)-6-cyclohexyl-3-[3-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1,2,4-oxadiazol-5- yl]hexanoate (Preparation 92) (400mg, 0.78mmol) in anhydrous tetrahydrofuran (3ml) was added and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a colourless oil (518mg) of approximately 70% purity which was used without further purification.

MS : 546 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.20 (2H, m), 3.80 (1H, t), 3.40 (1H, m), 3.25 (2H, d), 2.75 (1H, dd), 2.59 (1H, dd), 1.60-1.75 (7H, m), 1.43 (9H, s), 1.39 (9H, s), 1.10-1.30 (11H, m), 0.83 (2H, m).

Preparation 94:

(3R)-6-Cyclohexyl-3-[3-(3-ethoxy-3-oxopropyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



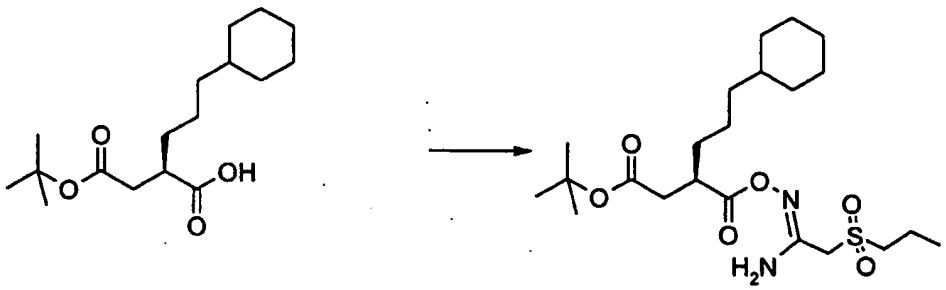
A solution of 1-tert-butyl 3-ethyl 2-({5-[(1R)-1-(2-tert-butoxy-2-oxoethyl)-4-cyclohexylbutyl]-1,2,4-oxadiazol-3-yl}methyl)malonate (Preparation 93) (510mg, 0.79mmol) in dichloromethane (10ml) was treated with trifluoroacetic acid (5ml) and stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene. The solid was dissolved in xylene (10ml) and heated at 140°C for 7 hours. The solvent was removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a gradient system of 95 : 5 : 0 (dichloromethane : isopropyl alcohol : acetic acid) gradually changing to 90 : 10 : 1 (dichloromethane : isopropyl alcohol : acetic acid) to afford the title compound as a colourless oil (117mg).

MS : 389 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 4.12 (2H, q), 3.48 (1H, m), 3.03 (2H, t), 2.92 (1H, dd), 2.75 (3H, m), 1.60-1.80 (7H, m), 1.10-1.35 (11H, m), 0.82 (2H, m).

Preparation 95:

tert-Butyl (3R)-3-[({[(Z)-1-amino-2-(propylsulfonyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate



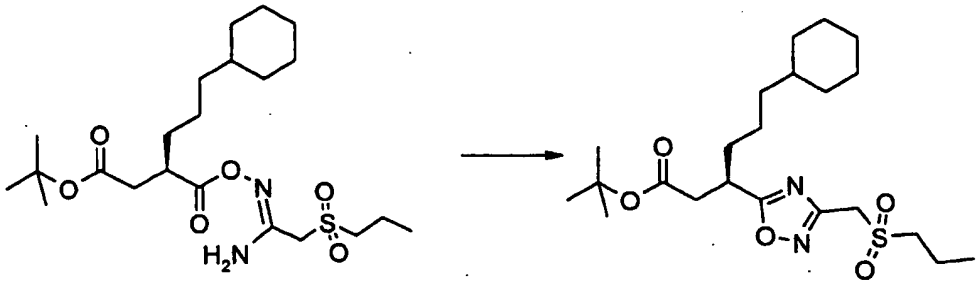
A solution of (2R)-2-(2-tert-butoxy-2-oxoethyl)-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.67mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (354mg, 1.85mmol), N-methylmorpholine (203 l, 1.85mmol) and 1-hydroxybenzotriazole hydrate (227mg, 1.67mmol) in dichloromethane (20ml) was treated with (1Z)-N'-hydroxy-2-(propylsulfonyl)ethanimidamide (300mg, 1.67mmol) and stirred at room temperature for 18 hours. The reaction mixture was diluted with water (10ml) and stirred for 20 minutes. The layers were separated via a 5 micron filter cartridge. The organic solvent was removed under reduced pressure to afford the title compound as a yellow solid (760mg).

MS : 483 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 5.62 (2H, br s), 3.82 (2H, d), 3.15 (2H, m), 2.83 (1H, m), 2.65 (1H, dd), 2.42 (1H, dd), 1.90 (2H, m), 1.57-1.80 (8H, m), 1.45 (9H, s), 1.10-1.30 (7H, m), 1.08 (3H, t), 0.83 (2H, m).

Preparation 96:

tert-Butyl (3R)-6-cyclohexyl-3-{3-[(propylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoate



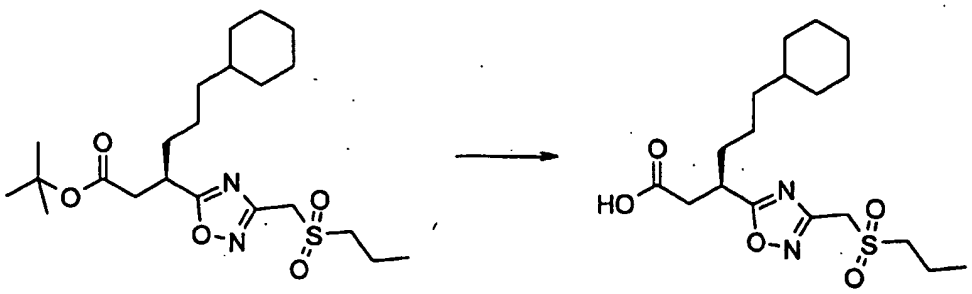
A solution of tert-butyl (3R)-3-[({[(Z)-1-amino-2-(propylsulfonyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate (Preparation 95) (760mg, 1.60mmol) in xylene (15ml) was heated at 130°C for 28 hours. After cooling to room temperature the reaction mixture was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 (pentane : ethyl acetate) gradually changing to 70 : 30 (pentane : ethyl acetate) to afford the title compound as a yellow oil (400mg).

MS : 441 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 4.32 (2H, s), 3.48 (1H, m), 3.13 (2H, dd), 2.80 (1H, dd), 2.65 (1H, dd), 1.92 (2H, m), 1.60-1.80 (7H, m), 1.40 (9H, s), 1.10-1.35 (11H, m), 0.82 (2H, m).

Preparation 97:

(3R)-6-Cyclohexyl-3-{3-[(propylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoic acid



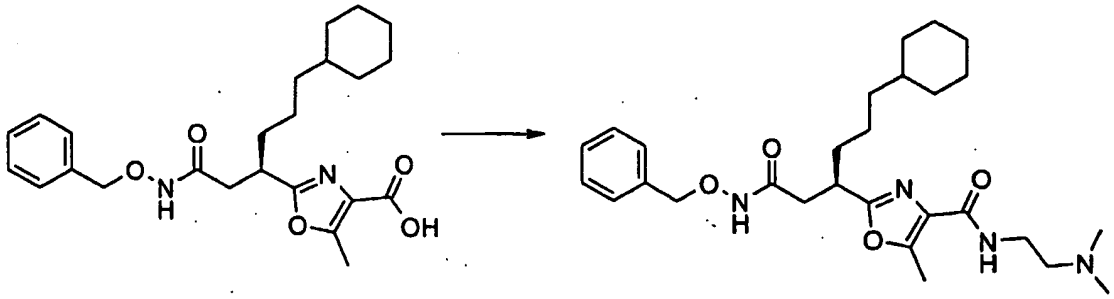
A solution of tert-butyl (3R)-6-cyclohexyl-3-{3-[(propylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}hexanoate (Preparation 96) (371mg, 0.84mmol) in hydrogen chloride in 1,4-dioxan (4M) (4ml) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure. The solid was dissolved in fresh hydrogen chloride in 1,4-dioxan (4M) and stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and the solvent was removed under reduced pressure to afford the title compound as a yellow oil (313mg).

MS : 385 $(M-H)^-$

^{1}H-NMR (DMSO) δ : 4.70 (2H, s), 3.43 (1H, m), 2.75 (2H, t), 2.52 (2H, obs), 1.75 (2H, m), 1.50-1.70 (7H, m), 1.05-1.30 (9H, m), 0.97 (3H, t), 0.80 (2H, m).

Preparation 98:

2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-N-[2-(dimethylamino)ethyl]-5-methyl-1,3-oxazole-4-carboxamide



A solution 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylic acid (Preparation 72) (200mg, 0.47mmol), N-methylmorpholine (77 l, 0.70mmol), 1-hydroxybenzotriazole hydrate (63mg, 0.47mmol)and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydochloride (134mg, 0.70mmol) in dichloromethane (10ml) was treated with N,N-dimethylethylenediamine (56 l, 0.51mmol) and stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane and washed with water, saturated sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a system of 94 : 4 : 0.4 (dichloromethane : methanol : ammonia) to afford the title compound as a white solid (216mg).

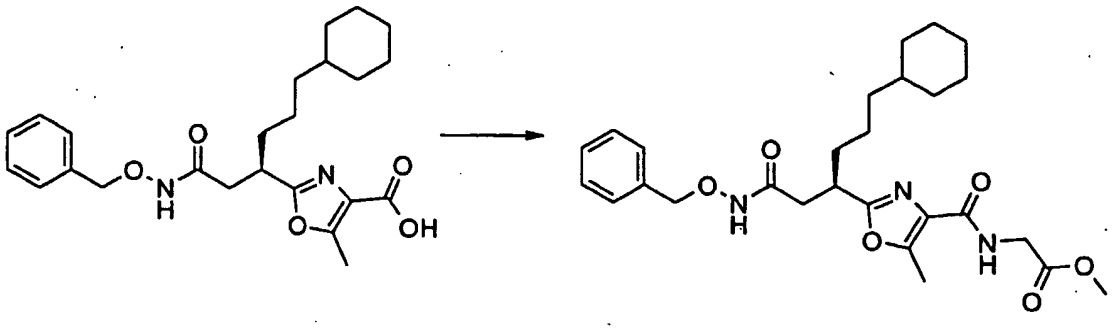
MS : 499 (MH^+)

Analysis : Found, C, 67.24; H, 8.60; N, 11.25%; $C_{28}H_{42}N_4O_4$ requires C, 67.44; H, 8.49; N, 11.24%

^{1}H-NMR ($CDCl_3$) δ : 7.35 (5H, br s), 7.10 (1H, br s), 4.85 (2H, s), 3.45 (2H, q), 3.35 (1H, m), 2.59 (3H, s), 2.46 (2H, t), 2.24 (6H, s), 1.60-1.75 (7H, m), 1.10-1.30 (7H, m), 0.85 (2H, m).

Preparation 99:

Methyl ({[2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazol-4-yl]carbonyl}amino)acetate



A solution 2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazole-4-carboxylic acid (Preparation 72) (230mg, 0.53mmol), N-methylmorpholine (61 l, 0.56mmol), 1-hydroxybenzotriazole hydrate (68mg, 0.53mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (107mg, 0.56mmol) in dichloromethane (10ml) was treated with

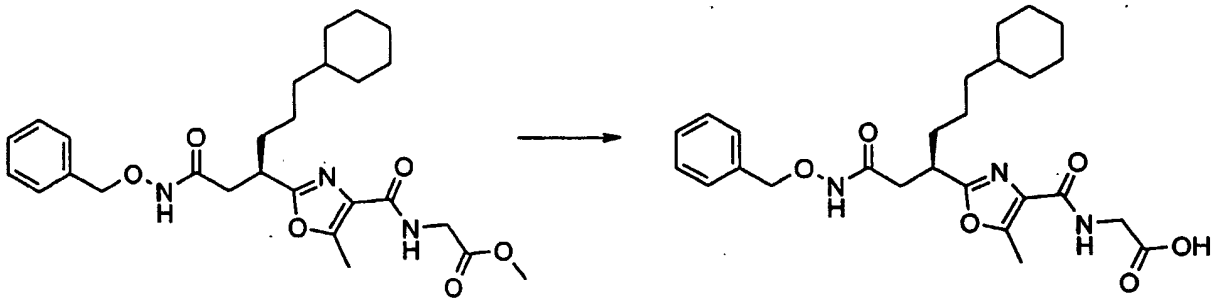
a solution of glycine methyl ester hydrochloride (70mg, 0.56mmol) and N-methylmorpholine (61 l, 0.56mmol) in dichloromethane (2ml) and stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane and washed with water, saturated sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of 100 : 0 : 0 (dichloromethane : methanol : ammonia) gradually changing to 98 : 2 : 0.2 (dichloromethane : methanol : ammonia) to afford the title compound as a white solid (160mg).

MS : 522 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 7.44 (1H, br s), 7.35 (5H, s), 5.11 (1H, s), 4.87 (2H, s), 4.12 (2H, d), 3.77 (3H, s), 3.37 (1H, m), 2.70 (1H, m), 2.56 (3H, s), 2.45 (1H, m), 1.55-1.1.80 (7H, m), 1.05-1.40 (8H, m), 0.83 (2H, m).

Preparation 100:

({[2-((1R)-1-{2-[(Benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazol-4-yl]carbonyl}amino)acetic acid



A solution of methyl ({[2-((1R)-1-{2-[(benzyloxy)amino]-2-oxoethyl}-4-cyclohexylbutyl)-5-methyl-1,3-oxazol-4-yl]carbonyl}amino)acetate (Preparation 99) (158mg, 0.32mmol) in 1,4-dioxan (5ml) was treated with sodium hydroxide solution (1M) (470 l, 0.47mmol). The mixture was stirred for 1 hour under a nitrogen atmosphere. The reaction mixture was diluted in water and washed with ethyl acetate. The aqueous layer was acidified with solid citric acid and extracted with ethyl acetate. The organic layers were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound (61mg).

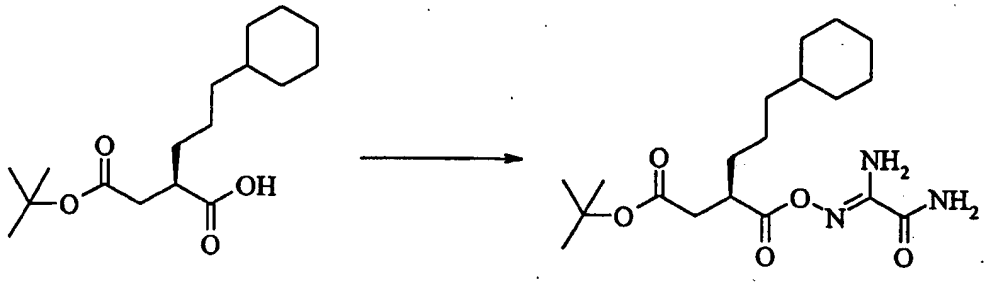
MS : 484 $(M-H)^-$

^{1}H-NMR ($CDCl_3$) δ : 7.35 (5H, br s), 4.85 (2H, s), 4.17 (2H, d), 3.39 (1H, m), 2.60 (3H, s), 2.43 (1H, m), 1.55-1.75 (7H, m), 1.10-1.35 (9H, m), 0.85 (2H, m).

Accurate Mass : 486.26 (MH^+)

Preparation 101:

tert-Butyl (3R)-3-[({[(Z)-1,2-diamino-2-oxoethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate



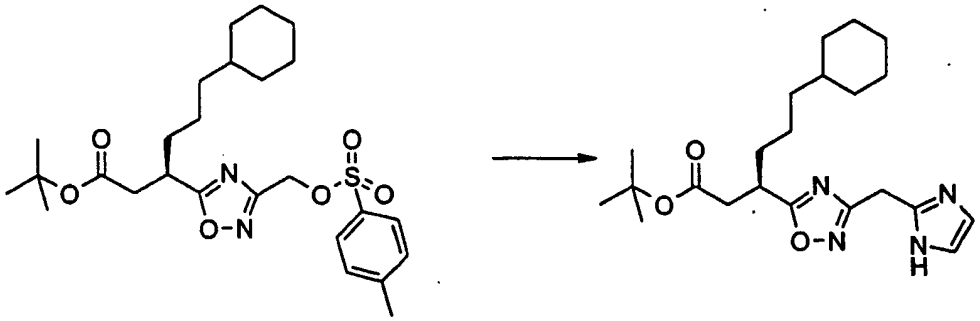
(*R*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid (Preparation 1) (3.47g, 11.6 mmol) in dimethylformamide (21 ml) was treated with 1,1'-carbonyldiimidazole (1.97g, 12.2 mmol) and the mixture was stirred at ambient temperature for 1 hour. N-Dimethylaminopyridine (1.43g, 11.7 mmol) was then added in one portion, followed by the addition of 2-amino-2-(hydroxyimino)acetamide (1.25g, 12.1 mmol, Helv.Chim.Acta; 47; 1964; 33-46). The resulting mixture was stirred at room temperature for 24 hours. The mixture was partitioned between ethyl acetate and a 10% solution of citric acid in demineralised water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with demineralised water (X4) and brine, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was crystallised from n-hexane, the precipitate was collected by filtration and dried *in vacuo* to afford the title compound as a colourless solid (3.30g, 74% yield).

MS : 382 $[(M-H)]^-$

^{1}H-NMR ($CDCl_3$) δ : 7.04 (1H, br s), 5.73 (2H, br s), 5.46 (1H, br s), 2.90 (1H, m), 2.68 (1H, dd, *J*= 15, 12 Hz), 2.45 (1H, dd, *J*= 18, 6 Hz), 1.63-1.74 (9H, m), 1.55-1.50 (1H, m), 1.43 (9H, s), 1.37-1.10 (5H, m), 0.93-0.82 (2H, m)

Preparation 102:

tert-butyl (3*R*)-6-cyclohexyl-3-[3-(1*H*-imidazol-2-ylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate



A solution of *tert*-butyl 1*H*-imidazole-1-carboxylate (133mg, 0.79mmol) in anhydrous tetrahydrofuran (2ml), cooled to -78°C, treated with *n*-butyl lithium, 2.5M in hexanes (320µl, 0.79mmol) and stirred under a nitrogen atmosphere for 1 hour. A solution of *tert*-butyl (3*R*)-6-cyclohexyl-3-[3-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1,2,4-oxadiazol-5- yl]hexanoate (Preparation 92) (400mg, 0.79mmol) in anhydrous tetrahydrofuran (2ml) was added slowly and the mixture was allowed to warm to room temperature and stirred at this temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate (30ml) and water (30ml). The organic layer was washed once more with water (20 ml), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a pale yellow oil (307mg).

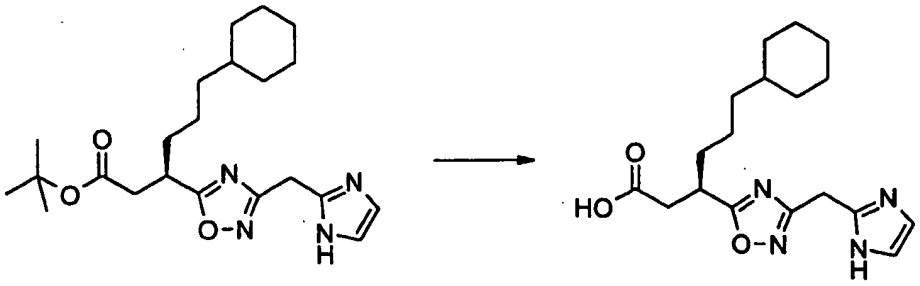
MS : 403 (MH^+)

Analysis : Found, C, 65.61; H, 8.91; N, 11.78%; $C_{22}H_{34}N_4O_3$ requires C, 65.64; H, 8.51; N, 13.92%

^{1}H-NMR ($CDCl_3$) δ : 7.59 (1H, s), 7.07 (1H, s), 7.01 (1H, s), 5.28 (2H, s), 3.40 (1H, m), 2.76 (1H, dd), 2.60 (1H, dd), 1.40-1.80 (10H, m), 1.10-1.40 (12H, m), 0.88 (4H, m).

Preparation 103:

(3*R*)-6-cyclohexyl-3-[3-(1*H*-imidazol-2-ylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



tert-butyl (3*R*)-6-cyclohexyl-3-[3-(1*H*-imidazol-2-ylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 102) (530mg, 1.32mmol) was treated with trifluoroacetic acid (10ml) and stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene (3x30ml) and dichloromethane (2x30ml) to afford the title compound (609mg).

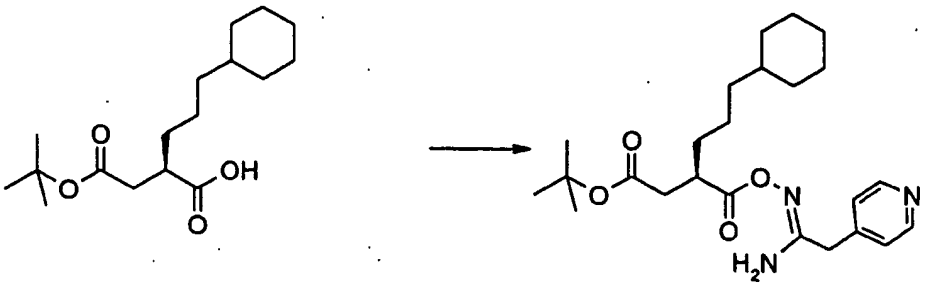
MS : 347 (MH^+)

Analysis : Found, C, 48.81; H, 5.61; N, 10.40%; $C_{18}H_{26}N_4O_3$. $1.5CF_3CO_2H$. $0.13H_2O$ requires C, 48.52; H, 5.38; N, 10.78%

^{1}H-NMR ($CDCl_3$) δ : 8.80 (1H, s), 7.38 (1H, s), 7.28 (1H, s), 5.41 (2H, s), 3.48 (1H, m), 2.70-2.95 (2H, m), 1.50-1.80 (7H, m), 1.10-1.40 (8H, m), 0.85 (2H, m).

Preparation 104:

tert-butyl (3*R*)-3-[({[(*Z*)-1-amino-2-(4-pyridinyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate



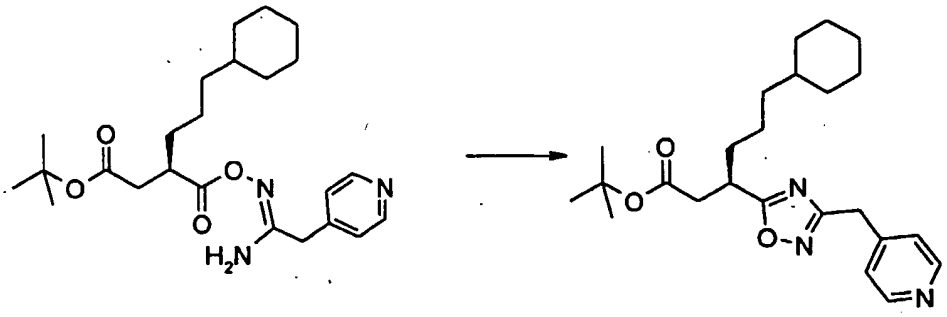
A solution of (2*R*)-2-(2-*tert*-butoxy-2-oxoethyl)-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.67mmol) in dichloromethane (20ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (354mg, 1.85mmol), *N*-methylmorpholine (203µl, 1.85mmol) and 1-hydroxybenzotriazole hydrate (227mg, 1.67mmol). (1*Z*)-*N*'-hydroxy-2-(4-pyridinyl)ethanimidamide (WO 9600720) (374mg, 1.67mmol) followed by *N*-methylmorpholine (369µl, 3.34mmol) were added to the reaction mixture which was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (10ml) and stirred for 20 minutes. The layers were separated via a 5 micron filter cartridge. The organic solvent was removed under reduced pressure to afford the title compound as a yellow oil (840mg). This was used without further purification in the following step.

MS : 454 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.58 (2H, d), 7.28 (2H, d), 4.90 (1H, br s), 3.57 (2H, s), 2.85 (1H, m), 2.40 (2H, m), 1.60-1.80 (6H, m), 1.30-1.60 (12H, m), 1.10-1.30 (6H, m), 0.87 (2H, m).

Preparation 105:

tert-butyl (3*R*)-6-cyclohexyl-3-[3-(4-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate



A solution of *tert*-butyl (3*R*)-3-[({[(*Z*)-1-amino-2-(4-pyridinyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate (Preparation 104) (840mg, 1.60mmol) in xylene (15ml) was heated at 130°C for 4.5 hours. After cooling to room temperature the reaction mixture was purified by column chromatography on silica gel eluting with a gradient system of 90 : 10 (pentane : ethyl acetate) gradually changing to 50 : 50 (pentane : ethyl acetate) to afford the title compound as a yellow oil (420mg).

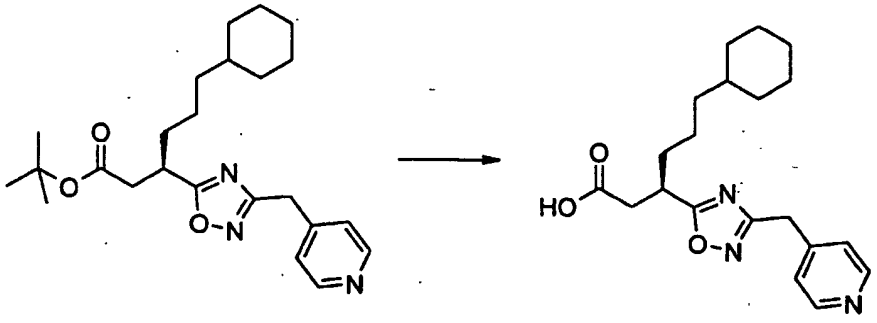
MS : 436 (MNa^+)

Analysis : Found, C, 69.38; H, 8.69; N, 9.72%; $C_{24}H_{35}N_3O_3$. 0.1EtOAc requires C, 69.39; H, 8.45; N, 9.72%

^{1}H-NMR ($CDCl_3$) δ : 8.54 (2H, d), 7.21 (2H, d), 4.03 (2H, s), 3.40 (1H, m), 2.77 (1H, dd), 2.60 (1H, m), 1.60-1.80 (8H, m), 1.35 (9H, s), 1.10-1.30 (7H, m), 0.82 (2H, m).

Preparation 106:

(3*R*)-6-cyclohexyl-3-[3-(4-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



A solution of *tert*-butyl (3*R*)-6-cyclohexyl-3-[3-(4-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 105) (400mg, 0.97mmol) in hydrogen chloride in 1,4-dioxan (4M) (5ml) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure. The solid was dissolved in fresh hydrogen chloride in 1,4-dioxan (4M) and stirred at room temperature for 3 hours. The solvent was removed under reduced pressure to afford the title compound as a yellow oil (390mg).

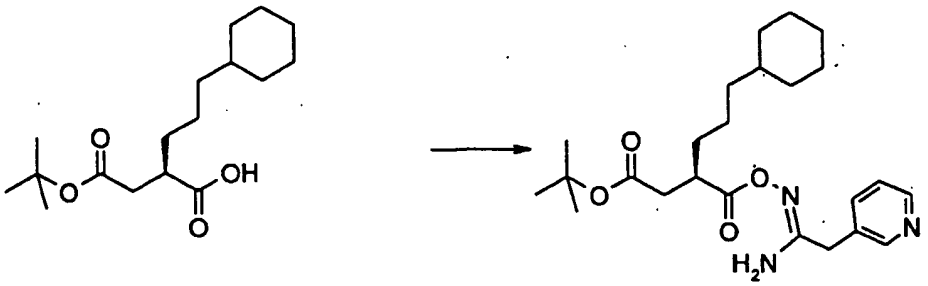
MS : 356 $(M-H)^-$

Analysis : Found, C, 59.65; H, 7.34; N, 9.62%; $C_{20}H_{27}N_3O_3$. HCl. 0.35H_2O. 0.25Dioxan requires C, 59.74; H, 7.33; N, 9.95%

^{1}H-NMR (DMSO) δ : 8.75 (2H, d), 7.78 (2H, d), 4.40 (2H, s), 3.40 (1H, m), 2.75 (2H, m), 1.50-1.70 (7H, m), 1.00-1.25 (8H, m), 0,89 (2H, m).

Preparation 107:

tert-butyl (3*R*)-3-[({[(*Z*)-1-amino-2-(3-pyridinyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate



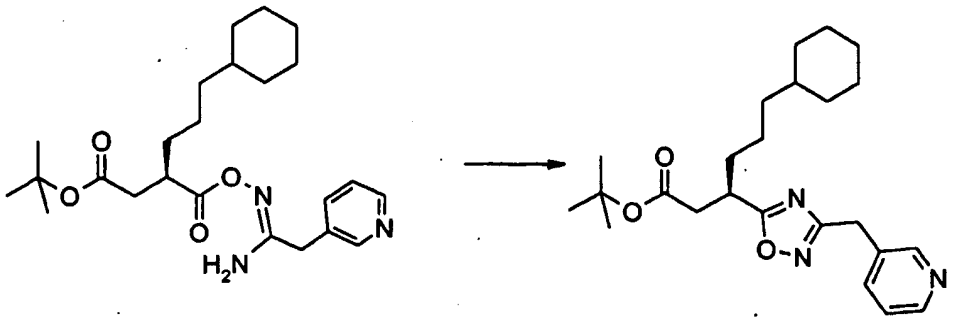
A solution of (2*R*)-2-(2-*tert*-butoxy-2-oxoethyl)-5-cyclohexylpentanoic acid (Preparation 1) (500mg, 1.67mmol) in dichloromethane (20ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (354mg, 1.85mmol), *N*-methylmorpholine (203µl, 1.85mmol) and 1-hydroxybenzotriazole hydrate (227mg, 1.67mmol). (1*Z*)-*N'*-hydroxy-2-(3-pyridinyl)ethanimidamide (WO 9600720) (374mg, 1.67mmol) followed by *N*-methylmorpholine (369µl, 3.34mmol) were added to the reaction mixture which was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (10ml) and stirred for 20 minutes. The layers were separated via a 5 micron filter cartridge. The organic solvent was removed under reduced pressure to afford the title compound as a yellow oil (835mg). This was used without further purification in the following step.

MS : 432 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.55 (2H, d), 7.70 (1H, d), 7.28 (1H, d), 4.90 (2H, br s), 3.70 (2H, m), 2.85 (1H, m), 2.40 (2H, m), 1.60-1.80 (7H, m), 1.40 (9H, s), 1.10-1.30 (8H, m), 0.83 (2H, m).

Preparation 108:

tert-butyl (3*R*)-6-cyclohexyl-3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate



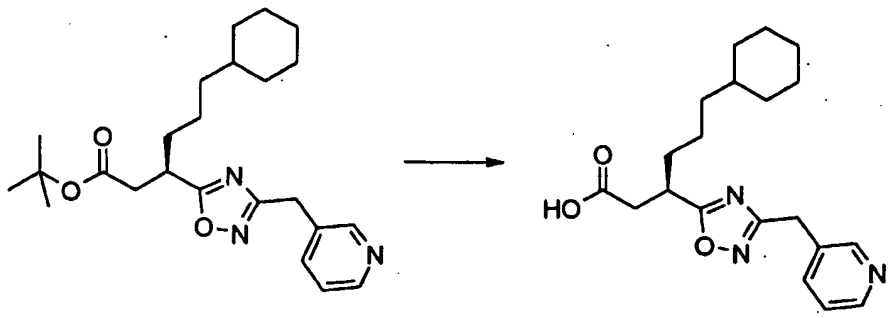
A solution of *tert*-butyl (3*R*)-3-[({[(*Z*)-1-amino-2-(3-pyridinyl)ethylidene]amino}oxy)carbonyl]-6-cyclohexylhexanoate (Preparation 107) (835mg, 1.60mmol) in xylene (15ml) was heated at 130°C for 4.5 hours. After cooling to room temperature the reaction mixture was purified by column chromatography on silica gel eluting with a gradient system of 90 : 10 (pentane : ethyl acetate) gradually changing to 50 : 50 (pentane : ethyl acetate) to afford the title compound as a yellow oil (443mg).

MS : 436 (MNa^+)

^{1}H-NMR ($CDCl_3$) δ : 8.60 (1H, s), 8.50 (1H, d), 7.62 (1H, d), 7.21 (1H, m), 4.05 (2H, s), 3.41 (1H, m), 2.77 (1H, dd), 2.58 (1H, m), 1.60-1.75 (8H, m), 1.35 (9H, s), 1.10-1.25 (7H, m), 0.82 (2H, m).

Preparation 109:

(3*R*)-6-cyclohexyl-3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoic acid



A solution of *tert*-butyl (3*R*)-6-cyclohexyl-3-[3-(3-pyridinylmethyl)-1,2,4-oxadiazol-5-yl]hexanoate (Preparation 108) (408mg, 0.99mmol) in hydrogen chloride in 1,4-dioxan (4M) (5ml) was stirred at room temperature for 18 hours. T.l.c. analysis showed reaction had gone >90%. A couple of drops of concentrated hydrochloric acid were added and the reaction mixture was stirred at

room temperature for a further 24 hours. The solvent was removed under reduced pressure. A fresh portion of hydrogen chloride in 1,4-dioxan (4M) (4ml) was added and stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and azeotroped with ethyl acetate and diethylether. The oil was dried under reduced pressure to afford the title compound as a yellow oil (418mg).

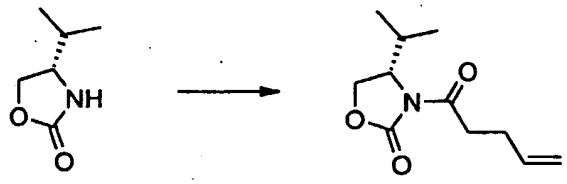
MS : 356 $(M-H)^-$

Analysis : Found, C, 59.07; H, 7.43; N, 8.71%; $C_{20}H_{27}N_3O_3$. HCl. $0.4H_2O$. 0.7Dioxan requires C, 59.17; H, 7.49; N, 9.08%

^{1}H-NMR (DMSO) δ :8.72 (1H, s), 8.63 (1H, d) 8.10 (1H, d), 7.69 (1H, t), 4.25 (2H, s), 3.38 (1H, m), 2.67 (2H, t), 1.50-1.70 (7H, m), 1.00-1.25 (8H, m), 0.79 (2H, m).

Preparation 110:

(4*S*)-4-isopropyl-3-(4-pentenoyl)-1,3-oxazolidin-2-one



A solution of (4*S*)-4-isopropyl-1,3-oxazolidin-2-one (26g, 0.2mol) in anhydrous tetrahydrofuran (600ml) was cooled to –78°C under a nitrogen atmosphere and treated with n-butyl lithium, 2.5M in hexanes (80ml, 0.2mol) keeping the temperature below –65°C. Once the addition was complete the reaction mixture was allowed to warm to -55°C and stirred at this temperature for 30 minutes. The mixture was cooled back down to -78°C and treated dropwise with a solution of 4-pentenoyl chloride (23.7g, 0.2mol) in anhydrous tetrahydrofuran (100ml). After stirring at -78°C for 30 minutes the reaction mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (1L) was added and the mixture was extracted with ethyl acetate (2x). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column

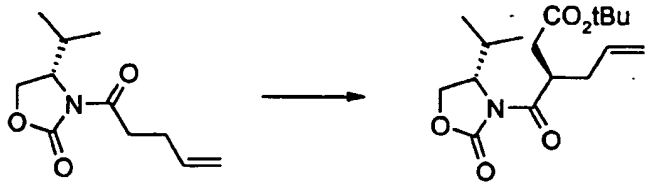
chromatography on silica gel eluting with a solvent gradient of 100 : 0 (pentane : ethyl acetate) gradually changing to 70 : 30 (pentane : ethyl acetate) to afford the title compound as a yellow oil (36.3g).

MS : 229 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 5.85 (1H, m), 5.10 (1H, d), 5.02 (1H, d), 4.41 (1H, m), 4.22 (2H, m), 3.11 (1H, m), 2.98 (1H, m), 2.30-2.45 (3H, m), 0.92 (3H, d), 0.85 (3H, d).

Preparation 111:

tert-butyl (3*R*)-3-{[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-5-hexenoate



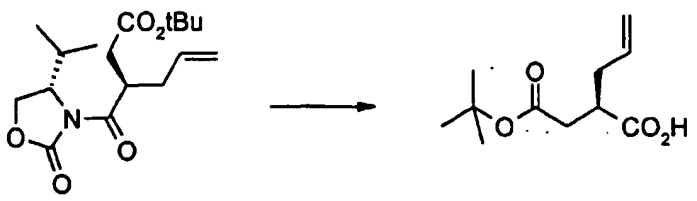
A solution of (4*S*)-4-isopropyl-3-(4-pentenoyl)-1,3-oxazolidin-2-one (Preparation 110) (36g, 0.17mol) in anhydrous tetrahydrofuran (650ml), under a nitrogen atmosphere, at -78°C, was treated dropwise with sodium bis(trimethylsilyl)amide, 1M in tetrahydrofuran (188ml, 0.19mol) over 1.5 hours, keeping the temperature below -65°C. The mixture was stirred at -78°C for 30 minutes and then allowed to warm to room temperature. The mixture was poured into saturated aqueous ammonium chloride solution (500ml) and extracted with diethylether. The organic extract was washed with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The brown slurry was triturated with hexane, filtered and washed with cold hexane. The white solid was dried under reduced pressure to afford the title compound (35.8g).

MS : 343 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 5.78 (1H, m), 5.08 (1H, d), 5.02 (1H, s), 4.40 (1H, m), 4.18-4.30 (3H, m), 2.77 (1H, dd), 2.30-2.45 (3H, m), 2.18 (1H, m), 1.41 (9H, s), 0.91 (6H, t).

Preparation 112:

(2*R*)-2-(4,4-dimethyl-2-oxopentyl)-4-pentenoic acid



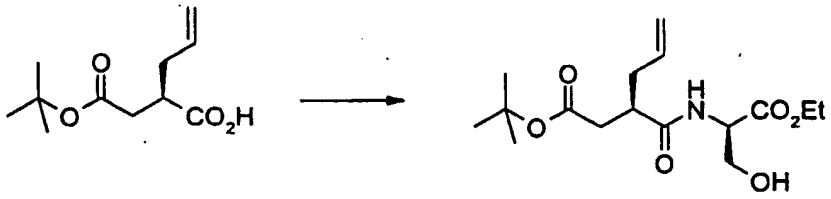
A solution of *tert*-butyl (3*R*)-3-{[(4*S*)-4-isopropyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-5-hexenoate (Preparation 111) (37.5g, 0.11mol) in 1,4-dioxan (190ml), under a nitrogen atmosphere, was treated with a solution of lithium hydroxide monohydrate (7.3g, 0.17mol) in water (75ml). The mixture was stirred at room temperature for 18 hours. Further lithium hydroxide monhydrate (2.42g, 0.06mol) was added and the mixture partitioned between ethyl acetate and water. The aqueous layer was acidified with hydrochloric acid (2M) (250ml) and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with 50 : 50 (pentane : ethyl acetate) to afford the title compound as a colourless oil (14.2g).

MS : 232 (MNH_4^+)

^{1}H-NMR ($CDCl_3$) δ : 5.77 (1H, m), 5.12 (1H, d), 5.08 (1H, s), 2.90 (1H, m), 2.60 (1H, dd), 2.25-2.55 (3H, m), 1.43 (9H, s).

Preparation 113:

ethyl (2*S*)-2-{[(2*R*)-2-(4,4-dimethyl-2-oxopentyl)-4-pentenoyl]amino}-3-hydroxypropanoate



A solution (2*R*)-2-(4,4-dimethyl-2-oxopentyl)-4-pentenoic acid (Preparation 112) (15.91g, 74.3mmol), 1-hydroxybenzotriazole hydrate (11.00g, 81.4mmol), L-serine ethylester hydrochloride (13.84g, 81.6mmol) and *N,N*-diisopropylethylamine (27ml, 156.0mmol) in dichloromethane (280ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15.67g, 81.7mmol) and stirred at room temperature for 18 hours under a nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and washed with water, aqueous citric acid (2M), saturated sodium hydrogen carbonate solution and brine, dried over

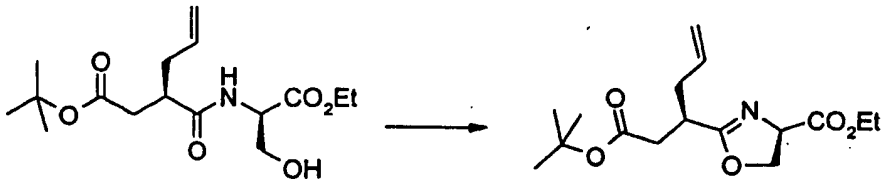
anhydrous sodium sulphate and filtered. The solvent was removed under reduced pressure to afford the title compound as a yellow oil (23.8g).

MS : 330 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 6.50 (1H, br d), 5.77 (1H, m), 5.10 (2H, s + d), 4.59 (1H, m), 4.22 (2H, q), 4.02 (1H, br d), 3.84 (1H, br d), 2.85 (1H, br s), 2.55-2.70 (2H, m), 2.40 (2H, m), 2.18 (1H, m), 1.40 (9H, s), 1.30 (3H, t).

Preparation 114:

ethyl (4*S*)-2-[(1*R*)-1-(4,4-dimethyl-2-oxopentyl)-3-butenyl]-4,5-dihydro-1,3-oxazole-4-carboxylate



A solution of ethyl (2*S*)-2-{[(2*R*)-2-(4,4-dimethyl-2-oxopentyl)-4-pentenoyl]amino}-3-hydroxypropanoate (Preparation 113) (23.8g, 72.3mmol) in anhydrous tetrahydrofuran (300ml), under a nitrogen atmosphere, was treated with (methoxycarbonylsulfamoyl)triethylammonium hydroxide triethylamine hydrochloride salt (43.5g, 79.4mmol) and stirred at reflux for 1.5 hours. After allowing to cool to room temperature the mixture was filtered, washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a solvent gradient of 80 : 20 (hexane : diethylether) gradually changing to 50 : 50 (hexane : diethylether) to afford the title compound as a colourless oil (11.0g).

MS : 312 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 5.73 (1H, m), 5.05 (2H, s + d), 4.66 (1H, m), 4.42 (1H, t), 4.38 (1H, t), 4.20 (2H, m), 3.95 (1H, m), 2.60 (1H, dd), 2.30-2.50 (3H, m), 1.41 (9H, s), 1.28 (3H, t).

Preparation 115:

ethyl 2-[(1*R*)-1-(4,4-dimethyl-2-oxopentyl)-3-butenyl]-1,3-oxazole-4-carboxylate

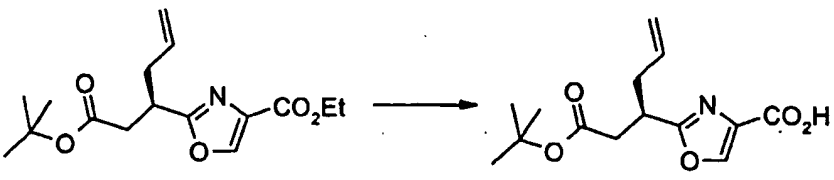
A suspension of copper (II) bromide (50.6g, 226.6mmol) and hexamethylenetetramine (31.6g, 225.5mmol) in dichloromethane (250ml), under a nitrogen atmosphere, was treated with 1,8-diazabicyco[5.4.0]undec-7-ene (33ml, 220.7mmol). The mixture was cooled to 0°C and treated with a solution of ethyl (4*S*)-2-[(1*R*)-1-(4,4-dimethyl-2-oxopentyl)-3-butenyl]-4,5-dihydro-1,3-oxazole-4-carboxylate (Preparation 114) (17.6g, 56.4mmol) in dichloromethane (250ml) via a cannula. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The solvent was removed under reduced pressure and the residue was azeotroped with ethyl acetate. The residue was dissolved in ethyl acetate and washed with a 1 : 1 mixture of 0.880 ammonia solution : saturated aqueous ammonium chloride solution (x2), water, hydrochloric acid (2M) (x3), saturated aqueous sodium hydrogen carbonate solution and brine. The solvent was removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a solvent gradient of 95 : 5 (hexane : diethylether) gradually changing to 50 : 50 (hexane : diethylether) to afford the title compound as a colourless oil (11.5g).

MS : 310 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.10 (1H, s), 5.70 (1H, m), 5.01 (2H, s + d), 4.37 (2H, q), 3.45 (1H, m), 2.79 (1H, dd), 2.50-2.65 (2H, m), 2.45 (1H, m), 1.30-1.45 (12H, s + t).

Preparation 116:

2-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-3-butenyl]-1,3-oxazole-4-carboxylic acid



Two identical reactions were put on each containing the following:

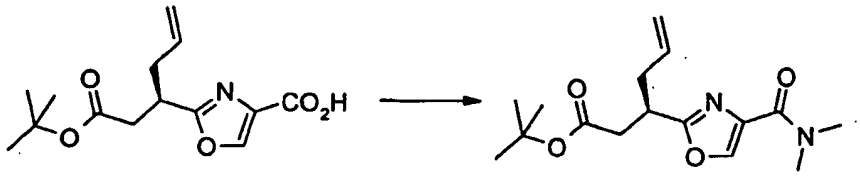
A solution of ethyl 2-[(1*R*)-1-(4,4-dimethyl-2-oxopentyl)-3-butenyl]-1,3-oxazole-4-carboxylate (Preparation 115) (4.0g, 12.9mmol) in 1,4-dioxan (40ml) and water (20ml) was cooled to 0°C and treated with lithium hydroxide monohydrate (0.8g, 19.0mmol). The mixture was stirred at 0°C for 4 hours. Further lithium hydroxide monhydrate (0.8g, 19.0mmol) was added and stirred at 0°C for 10 minutes. The two reactions were combined and partitioned between ethyl acetate and water. The aqueous layer was neutralised with citric acid (16.3g, 38.0mmol) and extracted with ethyl acetate (x3). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to afford the title compound as a colourless oil (8.3g).

MS : 282 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.10 (1H, s), 5.70 (1H, m), 5.01 (2H, s + d), 3.47 (1H, m), 2.80 (1H, dd), 2.62 (1H, dd), 2.57 (1H, m), 2.45 (1H, m), 1.38 (9H, s).

Preparation 117:

tert-butyl (3*R*)-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-hexenoate



A solution of 2-[(1*R*)-1-(2-*tert*-butoxy-2-oxoethyl)-3-butenyl]-1,3-oxazole-4-carboxylic acid (Preparation 116) (10.77g, 38.3mmol) in dichloromethane (250ml), at 0°C, was treated with 1-hydroxybenzotriazole hydrate (5.75g, 42.6mmol), dimethylamine hydrochloride (3.45g, 42.3mmol) and *N,N*-diisopropylethylamine (13ml, 75.13mmol) and lastly 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.10g, 42.3mmol), allowed to warm to room temperature and stirred for 20 hours under a nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution, aqueous citric acid (10%), water and brine, dried over anhydrous sodium sulphate and filtered. The solvent was removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a solvent gradient of 7 : 3 (pentane : ethyl acetate) gradually changing to 1 : 1 (pentane : ethyl acetate) to afford the title compound as a colourless oil (9.9g).

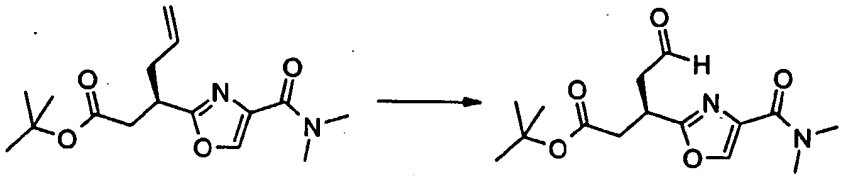
MS : 309 (MH^+)

Analysis : Found, C, 61.31; H, 7.89; N, 8.92%; $C_{18}H_{24}N_2O_4$. $0.2H_2O$ requires C, 61.60; H, 7.88; N, 8.98%

^{1}H-NMR ($CDCl_3$) δ : 8.00 (1H, s), 5.70 (1H, m), 5.02 (2H, s + d), 3.40 (1H, m), 3.30 (3H, br s), 3.03 (3H, br s), 2.75 (1H, m), 2.38 (1H, dd), 2.50 (1H, t), 2.43 (1H, m), 1.39 (9H, s).

Preparation 118:

tert-butyl (3*R*)-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-oxopentanoate



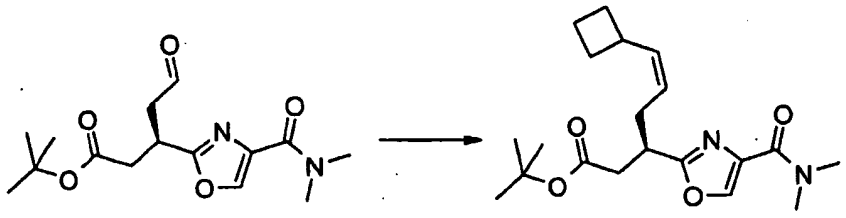
A solution of *tert*-butyl (3*R*)-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-hexenoate (Preparation 117) (1.0g, 3.24mmol) in acetone (20ml) and water (20ml) was treated with osmium tetroxide, 2.5%wt in *tert*-butanol (500μl, 0.04mmol) and stirred at room temperature for 5 minutes. Sodium periodate (2.13g, 10.00mmol) was added and the reaction mixture stirred for 2 hours. The reaction mixture was partitioned between ethyl acetate and aqueous sodium thiosulphate solution (20%wt). The organic layer was washed with water (x2) and brine, dried over anhydrous sodium sulphate and filtered. The solvent was removed under reduced pressure to afford the title compound as a colourless oil (866mg).
MS : 311 (MH^+)

Analysis : Found, C, 56.13; H, 7.13; N, 8.66%; $C_{15}H_{22}N_2O_5$. $0.6H_2O$ requires C, 56.10; H, 7.28; N, 8.72%

^{1}H-NMR ($CDCl_3$) δ : 9.78 (1H, s), 8.01 (1H, s), 3.87 (1H, m), 3.29 (3H, br s), 3.03 (4H, br s), 2.70-2.90 (2H, m), 2.64 (1H, dd), 1.39 (9H, s).

Preparation 119:

tert-butyl (3*R*,5*Z*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-hexenoate



A suspension of (cyclobutylmethyl)(triphenyl)phosphonium bromide (Preparation 122) (680mg, 1.65mmol) in anhydrous tetrahydrofuran (13ml), under a nitrogen atmosphere, at 0°C, was treated with sodium bis(trimethylsilyl)amide 1M in tetrahydrofuran (1.65ml, 1.65mmol) over a period of 5 minutes. The bright orange mixture was stirred at 0°C for 1 hour. A solution of *tert*-butyl (3*R*)-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-oxopentanoate (Preparation 118) (428mg, 1.38mmol) in toluene (4ml) was added to the mixture and stirred at 0°C for 30 minutes and allowed to warm to room temperature for a further 30 minutes. Water (2ml) was added and the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with dilute aqueous of potassium sodium tartrate solution and brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by column chromatography on silica gel eluting with a solvent gradient of 9 : 1 (hexane : ethyl acetate) gradually changing to 1 : 1 (hexane : ethyl acetate) to afford the title compound as a colourless oil (282mg).

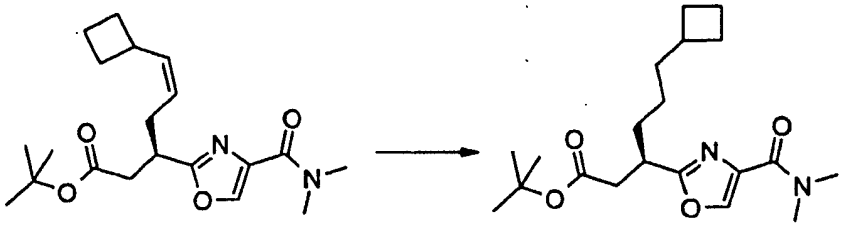
MS : 363 (MH^+)

Analysis : Found, C, 65.95; H, 8.35; N, 7.72%; $C_{20}H_{30}N_2O_4$. $0.1H_2O$ requires C, 65.95; H, 8.36; N, 7.69%

^{1}H-NMR ($CDCl_3$) δ : 8.00 (1H, s), 5.55 (1H, t), 5.11 (1H, q), 3.00-3.40 (8H, m), 2.73 (1H, dd), 2.56 (1H, dd), 2.30-2.50 (2H, m), 2.08 (2H, m), 1.70-1.90 (4H, m), 1.38 (9H, s).

Preparation 120:

tert-butyl (3*R*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}hexanoate



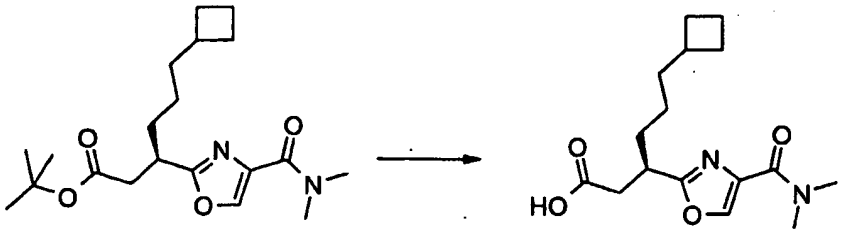
A solution of *tert*-butyl (3*R*,5*Z*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}-5-hexenoate (Preparation 119) (260mg, 0.72mmol) in ethanol (15ml) was treated with palladium hydroxide (250mg) followed by ammonium formate (500mg) and the mixture was stirred at reflux for 3 hours. The reaction mixture was allowed to cool to room temperature and was filtered through arbacel. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulphate and filtered. The solvent was removed under reduced pressure to afford the title compound as a colourless oil (246mg).

MS : 366 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.17 (1H, s), 3.31 (4H, m), 3.05 (3H, m), 2.70 (1H, dd), 2.59 (1H, dd), 2.22 (1H, m), 2.00 (2H, m), 1.60-1.90 (4H, m), 1.55 (2H, m), 1.30-1.40 (11H, m) 1.07 (2H, m).

Preparation 121:

(3*R*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}hexanoic acid



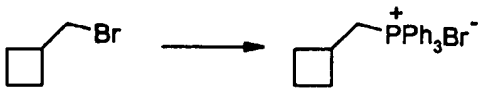
A solution of *tert*-butyl (3*R*)-6-cyclobutyl-3-{4-[(dimethylamino)carbonyl]-1,3-oxazol-2-yl}hexanoate (Preparation 120) (240mg, 0.66mmol) in dichloromethane (4ml) was treated with trifluoroacetic acid (1.2ml) and stirred at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue azeotroped from toluene and dichloromethane. The oil was purified by column chromatography on silica gel eluting with 97 : 3 : 0.3 (dichloromethane : methanol : acetic acid) to afford the title compound as a white solid (161mg).

MS : 309 (MH^+)

^{1}H-NMR ($CDCl_3$) δ : 8.05 (1H, s), 3.33 (4H, m), 3.05 (3H, m), 2.87 (1H, dd), 2.67 (1H, dd), 2.20 (1H, m), 1.99 (2H, m), 1.60-1.90 (4H, m), 1.52 (2H, m), 1.36 (2H, m) 1.07 (2H, m).

Preparation 122:

(cyclobutylmethyl)(triphenyl)phosphonium bromide



A solution of (bromomethyl)cyclobutane (4.5ml, 0.04mol) in toluene (50ml) was treated with triphenylphosphine (10.56g, 0.04mol) and the mixture stirred at reflux, under a nitrogen atmosphere, for 2 days. The mixture was allowed to cool to room temperature and treated with hexane (50ml). The solvent was decanted off and further hexane added. The solvent was decanted off again. The solid was washed with diethyl ether (x2) and dried under reduced pressure to afford the title compound as a white solid (6.34g).

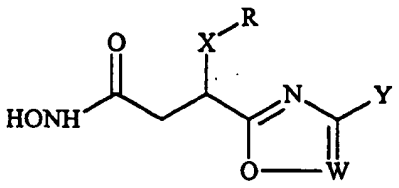
MS : 332 (MH^+)

Analysis : Found, C, 67.13; H, 5.88; N, 0.00%; $C_{23}H_{24}PBr$ requires C, 67.16; H, 5.88; N, 0.00%

^{1}H-NMR (d_6-DMSO) δ : 7.65-7.90 (15H, m), 3.74 (2H, m), 2.62 (1H, br m), 1.60-1.80 (6H, m).

CLAIMS

1. A compound of formula (I):



(I)

wherein:

X is C_{1-6} alkylene or C_{2-6} alkenylene, each of which is optionally substituted by one or more fluorine atoms;

R is aryl or C_{3-8} cycloalkyl optionally substituted by one or more fluorine atoms;

W is N or CZ;

Y and Z are each independently H,
C_{1-4} alkyl (optionally substituted by one or more substituents independently selected from halogen, $S(O)_pR^6$, OR^5, $CONR^1R^2$, CO_2R^7 and aryl),
C_{1-4} alkanoyl optionally substituted by one or more halogen,
C_{1-4} alkoxycarbonyl optionally substituted by one or more halogen,
or $CONR^1R^2$;

R^1 and R^2 are each independently selected from H, C_{3-8} cycloalkyl, C_{1-4} alkyl (optionally substituted by C_{3-8} cycloalkyl, aryl, CO_2H, CO_2R^5 and/or NR^3R^4),
or R^1 and R^2 can be taken together with the nitrogen to which they are attached to represent a 4- to 6-membered heterocyclic ring optionally containing one or two further hetero atoms in the ring independently selected from N, O and S,
which heterocyclic ring is optionally benzo- or pyrido-fused,
and which heterocyclic ring is optionally substituted by C_{1-4} alkyl, CO_2H, CO_2R^5, aryl and/or NR^3R^4;

R^3 and R^4 are each independently selected from H, C_1-C_4 alkyl or C_{1-4} alkoxycarbonyl optionally substituted by one or more halogen,
or R^3 and R^4 can be taken together with the nitrogen atom to which they are attached to represent a morpholine, piperidine, azetidine or piperazine (optionally N-substituted by C_{1-4} alkyl) moiety;

R^5 is C_{1-4} alkyl optionally substituted by CO_2R^7 or $CONR^3R^4$, or R^5 is aryl;

R^6 is C_{1-4} alkyl optionally substituted by one or more halogen, or aryl;

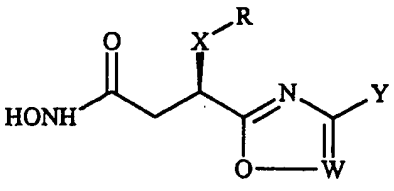
R^7 is H or R^6;

p is 0,1 or 2;

"Aryl" is a mono- or bicyclic aromatic carbocyclic or heterocyclic system comprising from 5 to 10 ring atoms, including up to 3 hetero-atoms selected from N, O and S,
where, if there is a N atom in the ring, it can be present as the N-oxide,
which ring system is optionally substituted by up to 3 substituents independently selected from halogen, C_{1-4} alkyl optionally substituted by one or more halogen, C_{1-4} alkoxy optionally substituted by one or more halogen, phenyl, pyridyl, CO_2H, $CONR^3R^4$, $CO_2(C_{1-4}$ alkyl), NR^3R^4, OH and $OC(O)(C_{1-4}$ alkyl);

and the pharmaceutically acceptable salts, solvates (including hydrates) and prodrugs thereof.

2. A compound, salt, solvate or prodrug according to claim 1 wherein the compound of formula (I) has the stereochemistry of formula (IA):



(IA)

3. A compound, salt, solvate or prodrug according to any previous claim wherein W is N.

4. A compound, salt, solvate or prodrug according to claim 1 or 2 where W is CZ, and at least one of Y and Z is H or C_{1-4} alkyl (optionally substituted by one or more halogen).

5. A compound, salt, solvate or prodrug according to claim 4 wherein W is CZ and Z is H or C_{1-4} alkyl optionally substituted by one or more halogen atoms.

6. A compound, salt, solvate or prodrug according to claim 5 wherein Z is H or methyl optionally substituted by one or more fluorine atoms.

7. A compound, salt, solvate or prodrug according to claim 6 wherein Z is H or methyl.

8. A compound, salt, solvate or prodrug according to any previous claim where X is a linear C_{2-4} alkylene moiety optionally substituted by one or more fluorine atoms.

9. A compound, salt, solvate or prodrug according to any previous claim where R is C_{3-8} cycloalkyl optionally substituted by one or more fluorine atoms.

10. A compound, salt, solvate or prodrug according to any previous claim where Y is C_{1-4} alkyl (optionally substituted by one or more substituents independently selected from halogen, $S(O)_pR^6$, OR^5, $CONR^1R^2$, CO_2R^7 and aryl), C_{1-4} alkoxycarbonyl, or $CONR^1R^2$.

11. A compound, salt, solvate or prodrug according to any previous claim wherein X is propylene.

12. A compound, salt, solvate or prodrug according to any previous claim wherein R is cyclobutyl or cyclohexyl optionally substituted by one or more fluorine atoms.

13. A compound, salt, solvate or prodrug according to any previous claim wherein Y is methyl, isopropyl, methoxymethyl, 2-methoxyethyl, (pyrrolidino)$COCH_2$, phenylsulphonylmethyl, 4-chlorophenoxymethyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, (imidazol-2-yl)methyl, $CO_2(C_{1-2}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl (optionally substituted by C_{3-8} cycloalkyl, aryl, CO_2H or CO_2R^5)), $CON(C_{1-4}$ alkyl)(C_{1-4} alkyl(optionally substituted by C_{3-8} cycloalkyl, aryl, CO_2H or CO_2R^5)), or $CONR^1R^2$ where R^1 and R^2 are taken together with the nitrogen to which they are attached to represent a 4- to 6-membered heterocyclic ring optionally containing one or two further hetero atoms in the ring independently selected from N, O and S,

and which heterocyclic ring is optionally benzo- or pyrido-fused,
and which heterocyclic ring is optionally substituted by C_{1-4} alkyl, CO_2H, CO_2R^5, aryl or NR^3R^4.

14. A compound, salt, solvate or prodrug according to any previous claim wherein R is cyclobutyl or cyclohexyl.

15. A compound, salt, solvate or prodrug according to any previous claim wherein Y is $CO_2C_2H_5$, $CONH_2$, $CONHCH_3$, $CONH(n\text{-}C_3H_7)$, $CONH(i\text{-}C_3H_7)$, (cyclopropyl)CH_2NHCO, (cyclobutyl)CH_2NHCO, (2-methoxyphenyl)CH_2NHCO, (4-methoxyphenyl)CH_2NHCO, (pyridin-2-yl)CH_2NHCO, $CONHCH_2CO_2H$, $CON(CH_3)CH_2CO_2CH_3$, $CON(CH_3)_2$, (4-dimethylaminopiperidinyl)CO, (3-morpholinoazetidinyl)CO, (4-(pyridin-4-yl)piperidino)CO, (pyridin-2-yl)$CH_2N(CH_3)CO$, $CON(CH_3)CH_2CO_2H$, (3-methoxycarbonylazetidinyl)CO, (3-carboxyazetidinyl)CO, methyl, isopropyl, methoxymethyl, 2-methoxyethyl, (pyrrolidino)$COCH_2$, phenylsulphonylmethyl, 4-chlorophenoxymethyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, (imidazol-2-yl)methyl, benzylaminocarbonyl, piperidinocarbonyl, (2,3-dihydroisoindol-2-yl)CO, (1,2,3,4-tetrahydroisoquinolin-2-yl)CO, morpholinocarbonyl, 4-methylpiperazinocarbonyl, (5-aza-1,2,3,4-tetrahydroisoquinolin-2-yl)CO or N-methylbenzylaminocarbonyl.

16. A compound, salt, solvate or prodrug according to any previous claim wherein R is cyclohexyl.

17. A compound, salt, solvate or prodrug according to any previous claim wherein Y is $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$.

18. A compound, or salt, solvate or prodrug thereof, of formula (I) according to claim 1 wherein the substituents are as specified in the compounds of the Examples described herein.

19. A compound according to claim 1 which is selected from:
5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-1,2,4-oxadiazole-3-carboxamide;
5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N-methyl-1,2,4-oxadiazole-3-carboxamide; and
5-{(1R)-4-cyclohexyl-1-[2-(hydroxyamino)-2-oxoethyl]butyl}-N,N-dimethyl-1,2,4-oxadiazole-3-carboxamide,
and the salts and solvates thereof.

20. A PCP inhibitor which is selective against MMP-1 and/or MMP-2 and/or MMP-9 and/or MMP-14.

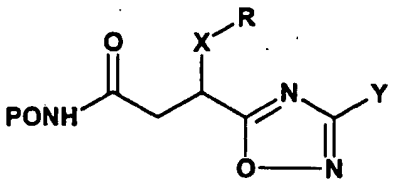
21. A substance according to any previous claim for use in medicine.

22. The use of a substance according to any of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 in the manufacture of a medicament for the treatment of a condition mediated by PCP.

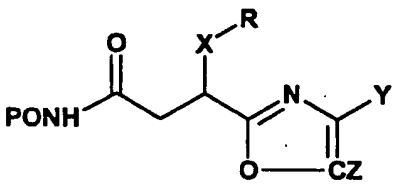
23. A pharmaceutical composition comprising a substance according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 and a pharmaceutically acceptable diluent, carrier or adjuvant.

24. A method of treatment of a condition mediated by PCP comprising administration of a therapeutically-effective amount of a substance according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

25. A process to make a compound of formula (I) as defined in claim (I) which comprises deprotection of a compound of formula (III) or (VIII),



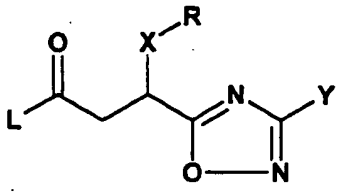
(III)



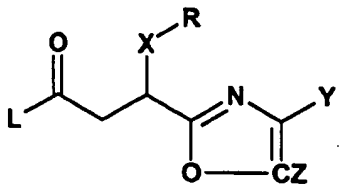
(VIII)

as appropriate, where P is an O-protecting group and the other substituents are as defined in claim 1.

26. A process to make a compound of formula (I) as defined in claim 1 which comprises reaction of a compound of formula (II) or (IX)



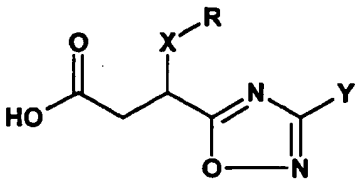
(II)



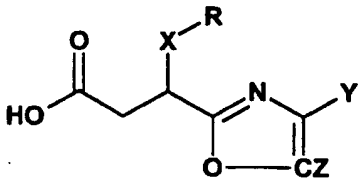
(IX)

as appropriate, wherein L is a suitable leaving group and the other substituents are as defined in claim 1, with hydroxylamine or a salt thereof, if necessary with a base.

27. A process for making a compound of formula (II) or (IX) as defined in claim 26 which comprises reaction of a compound of formula (IV) or (X) as appropriate



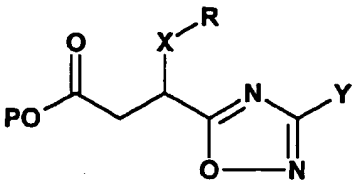
(IV)



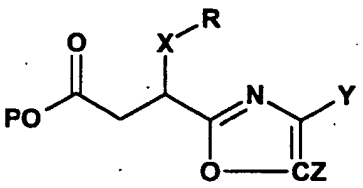
(X)

with a suitable activating reagent to introduce the "L" moiety.

28. A process to make a compound of formula (IV) or (X) as defined in claim 27 which comprises deprotecting a compound of formula (V) or (XI) as appropriate



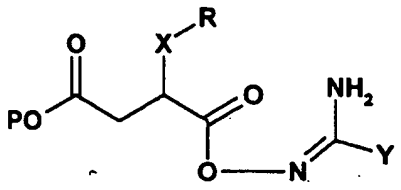
(V)



(XI)

where P is an O-protecting group.

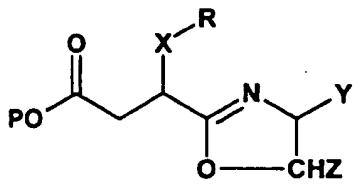
29. A process for making a compound of formula (V) as defined in claim 28 which comprises internal condensation of a compound of formula (VI)



(VI)

wherein P is an O-protecting group.

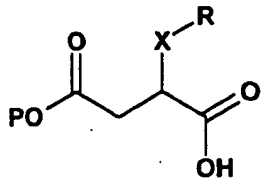
30. A process for making a compound of formula (XI) as defined in claim 28 which comprises dehydrogenation of a compound of formula (XII)



(XII)

wherein P is an O-protecting group.

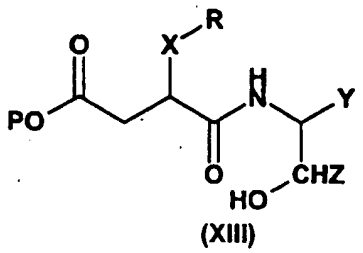
31. A process for making a compound of formula (VI) as defined in claim 29 which comprises reaction of a compound of formula (VII)



(VII)

with a compound of formula $YC(=NOH)NH_2$.

32. A process for making a compound of formula (XII) as defined in claim 30 which comprises internal condensation of a compound of formula (XIII):



(XIII)

33. A process for making a compound of formula (XIII) as defined in claim 32 which comprises condensation of a compound of formula (VII) as defined in claim 31 with a compound of formula $NH_2CH(Y)CH(Z)OH$.

34. A compound of formula (II) as defined in claim 26.

35. A compound of formula (III) as defined in claim 25.

36. A compound of formula (IV) as defined in claim 27.

37. A compound of formula (V) as defined in claim 28.

38. A compound of formula (VI) as defined in claim 29.

39. A compound of formula (VII) as defined in claim 31.

40. A compound of formula (VIII) as defined in claim 25.

41. A compound of formula (IX) as defined in claim 26.

42. A compound of formula (X) as defined in claim 27.

43. A compound of formula (XI) as defined in claim 28.

44. A compound of formula (XII) as defined in claim 30.

45. A compound of formula (XIII) as defined in claim 32.

46. (2R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid.

47. (4S)-4-benzyl-3-(5-cyclohexylpentanoyl)-1,3-oxazolidin-2-one.

48. tert-butyl 3-{[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-6-cyclohexylhexanoate

49. 2-[2-(tert-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid.

50. 3-(diethoxyphosphoryl)succinic acid 1-tert-butyl ester.

51. (E)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenyl-2-pentenoic acid.

52. (R)-2-[2-(tert-butoxy)-2-oxoethyl]-5-phenylpentanoic acid.

53. (*R*)-2-[2-(*tert*-butoxy)-2-oxoethyl]-5-cyclohexylpentanoic acid cyclohexylamine salt.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/IB 00/01855

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D271/06 C07D263/34 C07D413/06 C07D413/12 C07D413/14
C07D471/04 C07K5/078 A61K31/421 A61K31/422 A61K31/4245
A61P17/02 C07C69/08 C07F9/40 C07C259/14 C07C233/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMAMOTO M ET AL: "Inhibition of membrane-type 1 matrix metalloproteinase by hydroxamate inhibitors: an examination of the subsite pocket" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 8, 9 April 1998 (1998-04-09), pages 1209-1217, XP000867897 the whole document, particularly page 1210, scheme 1, method B, compounds 7, in combination with page 1211, table 1, compounds 1b and 1c	39,52
A	the whole document	1
	--- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2001	05. 06. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALLARD, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 00/01855

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/44 //(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEINMAN D H ET AL: "The design, synthesis, and structure-activity relationships of a series of macrocyclic MMP inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 16, 18 August 1998 (1998-08-18), pages 2087-2092, XP004137224 the whole document, particularly page 2091, table 1, compounds 12 and 13, in combination with page 2089, scheme 1 and penultimate alinea --- -/--	39

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALLARD, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/IB 00/01855

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VU C B ET AL: "Nonpeptidic SH2 Inhibitors of the Tyrosine Kinase ZAP-70" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 20, 18 October 1999 (1999-10-18), pages 3009-3014, XP004180527 the whole document, particularly page 3012, scheme 4 ---	39
X	MCCLURE K F ET AL: "Alkylation of succinates: synthesis of RO 32-3555" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 2, 20 January 1998 (1998-01-20), pages 143-146, XP004136833 the whole document, particularly page 144, compound 1 ---	39
X	EVANS D A ET AL: "A general method for the synthesis of enantiomerically pure beta-substituted, beta-amino acids through alpha-substituted succinic acid derivatives" JOURNAL OF ORGANIC CHEMISTRY, vol. 64, no. 17, 20 August 1999 (1999-08-20), pages 6411-6417, XP002163186 the whole document, particularly page 6415, compound 5d ---	39
X	SIMONEAU B ET AL: "Discovery of non-peptidic P2-P3 butanediamide renin inhibitors with high oral efficacy" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 7, no. 3, March 1999 (1999-03), pages 489-508, XP000990420 the whole document, particularly page 491, right-hand column, lines 11-15, page 492, scheme 4, compound 41, and page 501, left-hand column, penultimate alinea ---	39
X	FLOYD C D ET AL: "Rapid synthesis of matrix metalloproteinase inhibitors via Ugi four-component cndensation" SYNLETT, no. 6, June 1998 (1998-06), pages 637-639, XP002163187 cited in the application compounds 2j, 2k, 2m and 2n --- -/--	39,52

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1997:594709 XP002163188 RN 195509-70-7 and 195509-91-2 & WO 97 31892 A (SANKYO CO., LTD.) 4 September 1997 (1997-09-04) ---	45
X	WO 99 45927 A (SMITHKLINE BEECHAM CORPORATION) 16 September 1999 (1999-09-16) page 30, scheme X, compound 6 and step f, page 35, compound 8, pages 67 and 68, preparations 15d and 15e, and page 84, preparation 32f -----	28,42,43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/01855

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 24 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 20-24 (all partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-19, 20-24 (partly),25-49,52,53

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-19, 20-24 (partly), 25-49, 52, 53

   Ox(adi)azole-hydroxamic acids, their preparation and use and certain intermediates.

2. Claims: 50, 51

   Reagent and intermediate.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20-24 (all partly)

Present claim 20 and partly 21-24 (insofar they refer to claim 20) relates to compounds defined by reference to a desirable characteristic or property, namely their selectivity against certain matrix metalloproteinases (MMPs).

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that for said claims a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, said claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search for said claims over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds according to claims 1-19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible] onal Application No
PCT/IB 00/01855

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9731892 A	04-09-1997	AU 1812197 A	16-09-1997
		JP 9291072 A	11-11-1997
WO 9945927 A	16-09-1999	AU 2903399 A	27-09-1999
		EP 1061921 A	27-12-2000
		NO 20004503 A	10-10-2000
		TR 200002625 T	21-12-2000